EXHIBIT A

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Pharmaceutical Sales 2010

The following is a list of the top 200 pharmaceutical drugs by retail sales in 2010, listed by U.S. sales value and brand name.

New: Quarterly Top 100 prescription sales data now available, from Q1 2011 **more....**

Top 200 Drugs for 2010 by Sales

View data for: **2003** | **2004** | **2005** | **2006** | **2007** | **2008** | **2009** | 2010 | **2011** | **2012** **(By Units)**

Rank	Drug	Current Manufacturer	Total Sales ($000)	% Change 2009
1 (↑1)	**Nexium**	**AstraZeneca Pharmaceuticals LP**	5,276,153	4.9%
2 (↓1)	**Lipitor**	**Pfizer Inc.**	5,272,576	-2.3%
3	**Plavix**	**Bristol-Myers Squibb Company**	4,675,483	10.2%
4	**Advair Diskus**	**GlaxoSmithKline**	3,655,206	-1.0%
5 (↑3)	**OxyContin**	**Purdue Pharma LP**	3,554,751	13.1%
6	**Abilify**	**Bristol-Myers Squibb Company**	3,514,265	12.7%
7	**Singulair**	**Merck & Co., Inc.**	3,324,909	8.9%
8 (↓3)	**Seroquel**	**AstraZeneca Pharmaceuticals LP**	3,222,055	2.4%
9 (↑5)	**Crestor**	**AstraZeneca Pharmaceuticals LP**	2,922,687	27.0%
10 (↑1)	**Cymbalta**	**Eli Lilly and Company**	2,638,536	7.6%
11 (↓2)	**Actos**	**Takeda Pharmaceuticals U.S.A., Inc.**	2,631,930	4.2%
12 (↑1)	**Lexapro**	**Actavis Pharma, Inc.**	2,483,391	4.6%
13 (↑2)	**Zyprexa**	**Eli Lilly and Company**	2,036,092	7.7%
14 (↑9)	**Spiriva**	**Boehringer Ingelheim Pharmaceuticals, Inc.**	1,593,593	19.3%
15 (↑3)	**Lantus**	**Sanofi-Aventis U.S. LLC**	1,525,697	0.3%
16 (↑6)	**Aricept**	**Eisai Inc.**	1,522,517	13.3%
17 (↑2)	**Lyrica**	**Pfizer Inc.**	1,478,158	-0.1%
	Diovan	**Novartis Pharmaceuticals Corporation**	1,443,539	7.0%

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18 (↑6)				
19 (↓7)	Effexor XR	Pfizer Inc.	1,431,042	-40.1%
20 (↑7)	Concerta	Janssen Pharmaceuticals, Inc.	1,407,962	16.9%
21	Levaquin	Janssen Pharmaceuticals, Inc.	1,355,350	-0.6%
22 (↓2)	Celebrex	Pfizer Inc.	1,349,833	-6.9%
23 (↑2)	Diovan HCT	Novartis Pharmaceuticals Corporation	1,314,507	3.7%
24 (↑4)	Januvia	Merck & Co., Inc.	1,294,408	13.0%
25 (↑16)	Suboxone	Reckitt Benckiser Pharmaceuticals Inc.	1,164,872	26.6%
26 (↑14)	NovoLog	Novo Nordisk	1,101,447	20.6%
27 (↑9)	Viagra	Pfizer Inc.	1,028,769	5.5%
28 (↑4)	Atripla	Bristol-Myers Squibb Company	1,028,753	-6.5%
29 (↓3)	Tricor	Abbott Laboratories	1,015,682	-17.2%
30 (↑13)	Provigil	Cephalon, Inc.	999,975	6.7%
31 (↑2)	Zetia	Merck & Co., Inc.	985,823	-4.3%
32 (↑12)	Geodon oral	Pfizer Inc.	959,057	8.7%
33 (↓4)	Vytorin	Merck & Co., Inc.	953,625	-16.3%
34 (↑1)	Ambien CR	Sanofi-Aventis U.S. LLC	951,108	-2.5%
35 (↑11)	Lunesta	Sepracor Inc.	948,621	17.6%
36 (↑2)	Lidoderm	Endo Pharmaceuticals Inc.	934,418	-1.1%
37 (↑22)	Lantus SoloSTAR	Sanofi-Aventis U.S. LLC	933,589	50.5%
38 (↑15)	Vyvanse	Shire US, Inc.	931,421	40.9%
39 (↓5)	Aciphex	Eisai Inc.	915,796	-8.8%
40 (↑2)	Nasonex	Merck & Co., Inc.	886,446	-1.9%
41 (↓10)	Lovenox	Sanofi-Aventis U.S. LLC	867,240	-20.4%
42 (↓12)	Adderall XR	Shire US, Inc.	837,448	-27.0%
43 (↓4)	ProAir HFA	Teva Pharmaceuticals USA, Inc.	818,903	-12.6%
44 (↑1)	Truvada	Gilead Sciences, Inc.	813,944	-8.5%
45 (↑3)	Niaspan	Abbott Laboratories	793,882	11.0%

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46 (↑1)	Humalog	Eli Lilly and Company	783,294	3.2%
47 (↑8)	Cialis	Eli Lilly and Company	756,576	15.9%
48 (↑4)	Namenda	Actavis Pharma, Inc.	744,296	10.9%
49 (↑27)	Symbicort	AstraZeneca Pharmaceuticals LP	707,468	47.4%
50 (↑8)	Flovent HFA	GlaxoSmithKline	704,631	13.2%
51 (↑52)	Seroquel XR	AstraZeneca Pharmaceuticals LP	695,560	92.1%
52 (↑8)	Combivent	Boehringer Ingelheim Pharmaceuticals, Inc.	693,068	14.3%
53 (↑)	Lovaza	GlaxoSmithKline	682,384	15.5%
54 (↑24)	Solodyn	Medicis Pharmaceutical Corporation	673,427	40.7%
55 (↓6)	Detrol LA	Pfizer Inc.	620,231	-13.6%
56 (↑8)	AndroGel	Abbott Laboratories	593,780	10.1%
57 (↑10)	Benicar	Daiichi Sankyo	567,636	10.0%
58 (38)	Levemir	Novo Nordisk	567,341	41.1%
59 (2)	Enbrel	Amgen Inc.	546,814	-15.8%
60 (44)	Valtrex	GlaxoSmithKline	533,961	-69.9%
61 (2)	Benicar HCT	Daiichi Sankyo	526,177	-3.1%
62 (7)	Gleevec	Novartis Pharmaceuticals Corporation	517,967	-3.7%
63 (14)	Humira Pen	Abbott Laboratories	514,735	10.1%
64 (10)	Synthroid	Abbott Laboratories	506,859	2.5%
65 (20)	Xalatan	Pfizer Inc.	502,227	9.1%
66 (2)	Premarin tabs	Pfizer Inc.	497,757	-6.5%
67 (5)	Strattera	Eli Lilly and Company	496,960	-3.9%
68 (46)	Ventolin HFA	GlaxoSmithKline	496,659	65.4%
69 (52)	Flomax	Boehringer Ingelheim Pharmaceuticals, Inc.	486,106	-68.9%
70 (52)	Loestrin 24 Fe	Teva Pharmaceuticals USA, Inc.	483,754	82.3%
71 (13)	Protonix	Pfizer Inc.	481,429	3.5%
72 (1)	Boniva	Genentech, Inc.	480,470	-5.3%

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73 (22)	**Restasis**	**Actavis Pharma, Inc.**	480,414	19.0%
74 (14)	**Femara**	**Novartis Pharmaceuticals Corporation**	477,256	12.7%
75 (18)	**Enbrel Sureclick**	**Amgen Inc.**	474,602	2.6%
76 (17)	**NovoLog Mix 70/30**	**Novo Nordisk**	470,786	16.8%
77 (6)	**Evista**	**Eli Lilly and Company**	469,013	0.3%
78 (16)	**Byetta**	**Amylin Pharmaceuticals, Inc.**	459,454	-17.8%
79 (20)	**Janumet**	**Merck & Co., Inc.**	459,068	22.7%
80 (5)	**Asacol**	**Actavis Pharma, Inc.**	450,645	-8.3%
81 (9)	**Avodart**	**GlaxoSmithKline**	441,486	5.5%
82 (16)	**Vesicare**	**Astellas Pharma US, Inc.**	440,862	15.3%
83 (68)	**Trilipix**	**Abbott Laboratories**	428,978	104.5%
84 (3)	**Copaxone**	**Accredo Health Group, Inc.**	421,758	1.3%
85 (19)	**Focalin XR**	**Novartis Pharmaceuticals Corporation**	416,245	18.6%
86 (16)	**Reyataz**	**Bristol-Myers Squibb Company**	412,293	-20.9%
87 (37)	**Pristiq**	**Pfizer Inc.**	411,715	58.4%
88 (32)	**Arimidex**	**AstraZeneca Pharmaceuticals LP**	403,891	-37.5%
89 (9)	**Chantix**	**Pfizer Inc.**	394,944	-14.3%
90 (10)	**Sensipar**	**Amgen Inc.**	382,232	-0.5%
91 (3)	**Avapro**	**Bristol-Myers Squibb Company**	369,596	-6.2%
92 (49)	**Opana ER**	**Endo Pharmaceuticals Inc.**	366,417	52.5%
93 (43)	**Yaz**	**Bayer HealthCare Pharmaceuticals Inc.**	361,958	-49.1%
94 (27)	**Doryx**	**Actavis Pharma, Inc.**	361,662	35.7%
95 (13)	**Actoplus Met**	**Takeda Pharmaceuticals U.S.A., Inc.**	359,790	4.7%
96 (19)	**Humira**	**Abbott Laboratories**	358,012	-12.5%
97	**Avelox**	**Bayer HealthCare Pharmaceuticals Inc.**	353,130	-8.4%
98 (13)	**NuvaRing**	**Merck & Co., Inc.**	349,014	11.0%
99 ( )	**Renvela**	**Genzyme Corporation**	333,987	111.5%

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100 (35)	Ortho Tri-Cyclen Lo	Janssen Pharmaceuticals, Inc.	331,730	33.9%
101 (28)	Lamictal	GlaxoSmithKline	326,331	-35.2%
102 (4)	Avalide	Bristol-Myers Squibb Company	324,571	-6.4%
103 (1)	Xopenex	Akorn, Inc.	316,162	-13.0%
104 (18)	Actonel	Actavis Pharma, Inc.	313,904	-29.0%
105 ( )	Dexilant/Kapidex		313,386	254.8%
106 (4)	Lotrel	Novartis Pharmaceuticals Corporation	306,010	-6.8%
107 (9)	Invega	Janssen Pharmaceuticals, Inc.	304,182	5.1%
108 (24)	Welchol	Daiichi Sankyo	303,392	19.7%
109 (11)	Avonex	Biogen	303,147	0.2%
110 (73)	Topamax	Janssen Pharmaceuticals, Inc.	287,186	-70.5%
111 (1)	Norvir	Abbott Laboratories	287,102	-10.0%
112 (46)	Entocort EC	AstraZeneca Pharmaceuticals LP	282,547	38.6%
113 (15)	Aggrenox	Boehringer Ingelheim Pharmaceuticals, Inc.	277,144	6.5%
114 (51)	Travatan Z	Alcon	273,598	44.1%
115	Isentress	Merck & Co., Inc.	272,132	-9.8%
116 (25)	Avandia	GlaxoSmithKline	269,213	-33.8%
117	Prevacid SoluTab	Takeda Pharmaceuticals U.S.A., Inc.	268,284	-1.4%
118 (27)	Exforge	Novartis Pharmaceuticals Corporation	267,771	16.6%
119 (68)	Cozaar	Merck & Co., Inc.	267,081	-62.4%
120 (9)	Lumigan	Actavis Pharma, Inc.	267,047	7.0%
121 (12)	Caduet	Pfizer Inc.	266,967	-18.6%
122 (36)	Actonel 150	Actavis Pharma, Inc.	264,858	26.2%
123 (5)	Risperdal Consta	Janssen Pharmaceuticals, Inc.	262,054	-8.2%
124 (59)	Prograf	Astellas Pharma US, Inc.	260,885	-56.2%
125 (27)	Ciprodex otic	Alcon	254,888	13.8%
126 (23)	Vigamox	Alcon	252,864	11.3%

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127 (7)	Kadian	Actavis Pharma, Inc.	251,858	-0.8%
128 (2)	Coreg CR	GlaxoSmithKline	251,440	-1.6%
129 (4)	Levitra	Bayer HealthCare Pharmaceuticals Inc.	242,446	-5.9%
130 (8)	Maxalt	Merck & Co., Inc.	242,237	0.5%
131 (24)	Keppra	UCB, Inc.	241,737	-33.0%
132 (122)	Prevacid	Takeda Pharmaceuticals U.S.A., Inc.	241,374	-90.6%
133 (27)	Micardis	Boehringer Ingelheim Pharmaceuticals, Inc.	238,335	23.9%
134 ( )	Bystolic	Actavis Pharma, Inc.	231,449	72.2%
135 (28)	Prezista	Janssen Biotech, Inc.	230,406	13.8%
136 (52)	Exelon Patch	Novartis Pharmaceuticals Corporation	229,601	38.2%
137 ( )	Nuvigil	Cephalon, Inc.	223,885	239.6%
138 (2)	Zyvox	Pfizer Inc.	222,554	-7.5%
139 (41)	Lialda	Shire US, Inc.	222,201	29.3%
140 (15)	Epzicom	GlaxoSmithKline	221,406	-17.0%
141 (20)	Enablex	Actavis Pharma, Inc.	220,478	11.0%
142 (19)	Forteo	Eli Lilly and Company	219,387	-25.1%
143 (7)	Viread	Gilead Sciences, Inc.	216,264	-6.2%
144 (31)	Kaletra	Abbott Laboratories	212,723	-32.9%
145 (17)	Micardis HCT	Abbott Laboratories	211,575	10.4%
146 (8)	Maxalt MLT	Merck & Co., Inc.	211,230	-1.1%
147	Humalog Mix 75/25 Pen	Eli Lilly and Company	211,021	-6.9%
148 (12)	Xeloda	Genentech, Inc.	209,499	-11.7%
149 (7)	Asmanex	Merck & Co., Inc.	208,839	3.8%
150 (84)	Hyzaar	Merck & Co., Inc.	207,471	-62.3%
151 (20)	Fentora	Cephalon, Inc.	207,376	11.2%
152 (91)	Pulmicort Respules	AstraZeneca Pharmaceuticals LP	205,218	-68.0%
153 ( )	Ranexa	Gilead Sciences, Inc.	200,622	41.5%

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154 (49)	**RenaGel**	**Genzyme Corporation**	199,275	-48.2%
155 (34)	**Prempro**	**Pfizer Inc.**	198,132	22.2%
156 (1)	**Relpax**	**Pfizer Inc.**	197,341	-3.4%
157 (12)	**Patanol**	**Alcon**	196,500	2.6%
158 (8)	**Amitiza**	**Takeda Pharmaceuticals U.S.A., Inc.**	195,132	1.4%
159 (4)	**Duragesic**	**Johnson & Johnson**	194,599	-14.5%
160 ( )	**Vancocin HCl**	**Eli Lilly and Company**	192,066	23.4%
161 (22)	**Nasacort AQ**	**Sanofi-Aventis U.S. LLC**	192,035	-19.0%
162 (35)	**Proventil HFA**	**Merck & Co., Inc.**	191,839	-26.5%
163 ( )	**Advair HFA**	**GlaxoSmithKline**	191,245	26.4%
164 (14)	**Valcyte**	**Genentech, Inc.**	191,160	-0.9%
165 (21)	**Wellbutrin XL**	**Valeant Pharmaceuticals International, Inc.**	189,026	-21.2%
166 ( )	**Oracea**	**Galderma Laboratories, L.P.**	187,182	67.9%
167 (18)	**Vivelle-DOT**	**Novartis Pharmaceuticals Corporation**	185,860	12.4%
168 (11)	**Uroxatral**	**Concordia Pharmaceuticals Inc.**	185,624	6.2%
169 (8)	**Zovirax topical**	**GlaxoSmithKline**	184,377	2.6%
170 (27)	**Epipen**	**King Pharmaceuticals, Inc.**	182,785	20.8%
171 ( )	**Creon**	**Abbott Laboratories**	181,303	358.6%
172 ( )	**Azor**	**Daiichi Sankyo**	179,647	33.0%
173 (9)	**Pentasa**	**Sanofi-Aventis U.S. LLC**	178,068	4.5%
174 (32)	**Procrit**	**Janssen Biotech, Inc.**	174,622	-25.9%
175 ( )	**Pataday**	**Alcon**	173,553	25.5%
176 (30)	**Differin**	**Galderma Laboratories, L.P.**	171,454	-24.8%
177 (10)	**Premarin vaginal**	**Pfizer Inc.**	170,860	3.5%
178 ( )	**Zyprexa Zydis**	**Eli Lilly and Company**	169,714	6.7%
179 (36)	**Tussionex**	**Sanofi-Aventis U.S. LLC**	169,611	-29.8%
180 ( )	**Victoza**	**Novo Nordisk**	168,943	0.0%

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181 ( )	**Humalog KwikPen**	**Eli Lilly and Company**	168,270	79.6%
182 ( )	**Arixtra**	**GlaxoSmithKline**	165,530	19.9%
183 ( )	**Qvar**	**Janssen Pharmaceuticals, Inc.**	163,697	41.1%
184 (36)	**Combivir**	**GlaxoSmithKline**	163,406	-27.8%
185 ( )	**Testim**	**Endo Pharmaceuticals Inc.**	163,015	12.2%
186 (60)	**Tarceva**	**Astellas Pharma US, Inc.**	160,591	-38.2%
187 (17)	**Xyzal**	**Sanofi-Aventis U.S. LLC**	160,237	-15.6%
188 (12)	**Elmiron**	**Janssen Pharmaceuticals, Inc.**	158,274	4.3%
189 (5)	**Propecia**	**Merck & Co., Inc.**	157,892	-5.7%
190 (108)	**CellCept**	**Genentech, Inc.**	157,743	-68.3%
191 (110)	**Skelaxin**	**Elan Corporation, plc**	156,372	-67.7%
192 ( )	**Betaseron**	**Bayer HealthCare Pharmaceuticals Inc.**	155,952	-6.8%
193 (12)	**Temodar**	**Merck & Co., Inc.**	154,466	-14.9%
194 ( )	**Flector**	**Actavis Pharma, Inc.**	153,814	0.2%
195 (27)	**Pegasys**	**Genentech, Inc.**	153,101	-8.4%
196 (6)	**Prandin**	**Novo Nordisk**	151,678	-5.9%
197 (5)	**Veramyst**	**GlaxoSmithKline**	150,582	-7.8%
198 ( )	**Intuniv**	**Shire US, Inc.**	150,346	NA
199 ( )	**Clobex**	**Galderma Laboratories, L.P.**	150,230	20.6%
200 ( )	**Humulin N**	**Eli Lilly and Company**	149,945	4.4%

Source: Verispan, VONA

View data for: **2003** | **2004** | **2005** | **2006** | **2007** | **2008** | **2009** | 2010 | **2011** | **2012** **(By Units)**

EXHIBIT B

[redacted]

SUBOXONE (CIII)
(buprenorphine HCl and naloxone HCl dihydrate sublingual tablets)

SUBUTEX (CIII)
(buprenorphine HCl sublingual tablets)

Rx only

Under the Drug Addiction Treatment Act of 2000 (DATA) codified at 21 U.S.C. 823(g), prescription use of this product in the treatment of opioid dependence is limited to physicians who meet certain qualifying requirements, and have notified the Secretary of Health and Human Services (HHS) of their intent to prescribe this product for the treatment of opioid dependence.

DESCRIPTION

SUBOXONE sublingual tablets contain buprenorphine HCl and naloxone HCl dihydrate at a ratio of 4:1 buprenorphine: naloxone (ratio of free bases).

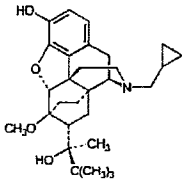
SUBUTEX sublingual tablets contain buprenorphine HCl.

Buprenorphine is a partial agonist at the mu-opioid receptor and an antagonist at the kappa-opioid receptor. Naloxone is an antagonist at the mu-opioid receptor.

Buprenorphine is a Schedule III narcotic under the Controlled Substances Act.

Buprenorphine hydrochloride is a white powder, weakly acidic with limited solubility in water (17mg/mL). Chemically, buprenorphine is 17-(cyclopropylmethyl)-α-(1,1-dimethylethyl)-4, 5-epoxy-18, 19-dihydro-3-hydroxy-6-methoxy-α-methyl-6, 14-ethenomorphinan-7-methanol, hydrochloride [5α, 7α(S)]-. Buprenorphine hydrochloride has the molecular formula $C_{29}H_{41}NO_4$ HCl and the molecular weight is 504.10.

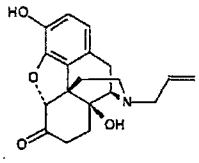
STRUCTURAL FORMULA OF BUPRENORPHINE



.HCl

Naloxone hydrochloride is a white to slightly off-white powder and is soluble in water, in dilute acids and in strong alkali. Chemically, naloxone is 17-Allyl-4,5 α -epoxy-3, 14-dihydroxymorphinan-6-one hydrochloride. Naloxone Hydrochloride has the molecular formula $C_{19}H_{21}NO_4$ HCl .$2H_2O$ and the molecular weight is 399.87.

STRUCTURAL FORMULA OF NALOXONE



.HCl

SUBOXONE is an uncoated **hexagonal orange tablet** intended for sublingual administration. It is available in two dosage strengths, 2mg buprenorphine with 0.5mg naloxone, and 8mg buprenorphine with 2mg naloxone free bases. Each tablet also contains lactose, mannitol, cornstarch, povidone K30, citric acid, sodium citrate, FD&C Yellow No.6 color, magnesium stearate, and the tablets also contain Acesulfame K sweetener and a lemon / lime flavor.

SUBUTEX is an uncoated **oval white tablet** intended for sublingual administration. It is available in two dosage strengths, 2mg buprenorphine and 8mg buprenorphine free base. Each tablet also contains lactose, mannitol, cornstarch, povidone K30, citric acid, sodium citrate and magnesium stearate.

CLINICAL PHARMACOLOGY

Subjective Effects:
Comparisons of buprenorphine with full agonists such as methadone and hydromorphone suggest that sublingual buprenorphine produces typical opioid agonist effects which are limited by a ceiling effect.

In non-dependent subjects, acute sublingual doses of SUBOXONE tablets produced opioid agonist effects, which reached a maximum between doses of 8 mg and 16mg of SUBUTEX. The effects of 16mg SUBOXONE were similar to those produced by 16mg SUBUTEX (buprenorphine alone).

Opioid agonist ceiling effects were also observed in a double-blind, parallel group, dose ranging comparison of single doses of buprenorphine sublingual solution (1, 2, 4, 8, 16, or 32 mg), placebo, and a full agonist control at various doses. The treatments were given in ascending dose order at intervals of at least one week to 16 opioid-experienced, non-dependent subjects. Both drugs produced typical opioid agonist effects. For all the measures for which the drugs produced an effect, buprenorphine produced a dose-related response but, in each case, there was a dose that produced no further effect. In contrast, the highest dose of the full agonist control always produced the greatest effects. Agonist objective rating scores remained elevated for the higher doses of buprenorphine (8-32 mg) longer than for the lower doses and did not return to baseline until 48 hours after drug administrations. The onset of effects appeared more rapidly with buprenorphine than with the full agonist control, with most doses nearing peak effect after 100 minutes for buprenorphine compared to 150 minutes for the full agonist control.

Physiologic Effects:
Buprenorphine in intravenous (2mg, 4mg, 8mg, 12mg and 16 mg) and sublingual (12mg) doses has been administered to non-dependent subjects to examine cardiovascular, respiratory and subjective effects at doses comparable to those used for treatment of opioid dependence. Compared with placebo, there were no statistically significant differences among any of the treatment conditions for blood pressure, heart rate, respiratory rate, O_2 saturation or skin temperature across time. Systolic BP was higher in the 8 mg group than placebo (3 hour AUC values). Minimum and maximum effects were similar across all treatments. Subjects remained responsive to low voice and responded to computer prompts. Some subjects showed irritability, but no other changes were observed.

The respiratory effects of sublingual buprenorphine were compared with the effects of methadone in a double-blind, parallel group, dose ranging comparison of single doses of buprenorphine sublingual solution (1, 2, 4, 8, 16, or 32 mg) and oral methadone (15, 30, 45, or 60 mg) in non-dependent, opioid-experienced volunteers. In this study, hypoventilation not requiring medical intervention was reported more frequently after buprenorphine doses of 4 mg and higher than after methadone. Both drugs decreased O_2 saturation to the same degree.

Effect of Naloxone:
Physiologic and subjective effects following acute sublingual administration of SUBOXONE and SUBUTEX tablets were similar at equivalent dose levels of buprenorphine. Naloxone, in the SUBOXONE formulation, had no clinically significant effect when administered by the sublingual route, although blood levels of the drug were measurable. SUBOXONE, when administered sublingually even to an opioid-dependent population, was recognized as an opioid agonist, whereas when administered intramuscularly, combinations of buprenorphine with naloxone produced opioid antagonist actions similar to naloxone. In methadone-maintained patients and heroin-dependent subjects, intravenous administration of buprenorphine/naloxone combinations precipitated opioid withdrawal and was perceived as unpleasant and dysphoric. In morphine-stabilized subjects, intravenously administered combinations of buprenorphine with naloxone produced opioid antagonist and withdrawal effects that were ratio-dependent; the most intense withdrawal effects were produced by 2:1 and 4:1 ratios, less intense by an 8:1 ratio. SUBOXONE tablets contain buprenorphine with naloxone at a ratio of 4:1.

Pharmacokinetics:
Absorption:
Plasma levels of buprenorphine increased with the sublingual dose of SUBUTEX and SUBOXONE, and plasma levels of naloxone increased with the sublingual dose of SUBOXONE (Table 1). There was a wide inter-patient variability in the sublingual absorption of buprenorphine and naloxone, but within subjects the variability was low. Both C_{max} and AUC of buprenorphine increased in a linear fashion with the increase in dose (in the range of 4 to 16 mg), although the increase was not directly dose-proportional.

Naloxone did not affect the pharmacokinetics of buprenorphine and both SUBUTEX and SUBOXONE deliver similar plasma concentrations of buprenorphine. The levels of naloxone were too low to assess dose-proportionality. At the three naloxone doses of 1 mg, 2 mg, and 4 mg, levels above the limit of quantitation (0.05 ng/mL) were not detected beyond 2 hours in seven of eight subjects. In one individual, at the 4mg dose, the last measurable concentration was at 8 hours. Within each subject (for most of the subjects), across the doses there was a trend toward an increase in naloxone concentrations with increase in dose. Mean peak naloxone levels ranged from 0.11 to 0.28ng/mL in the dose range of 1-4 mg.

Table 1. Pharmacokinetic parameters of buprenorphine after the administration of 4 mg, 8mg, and 16 mg Suboxone® doses and 16mg Subutex® dose (mean (%CV)).

Pharmacokinetic Parameter	Suboxone® 4 mg	Suboxone® 8 mg	Suboxone® 16 mg	Subutex® 16 mg
C_{max}, ng/mL	1.84 (39)	3.0 (51)	5.95 (38)	5.47 (23)
AUC_{0-48}, hour. ng/mL	12.52 (35)	20.22 (43)	34.89 (33)	32.63 (25)

Distribution:
Buprenorphine is approximately 96% protein bound, primarily to alpha and beta globulin.

Naloxone is approximately 45% protein bound, primarily to albumin.

Metabolism:
Buprenorphine undergoes both N-dealkylation to norbuprenorphine and glucuronidation. The N-dealkylation pathway is mediated by cytochrome P-450 3A4 isozyme. Norbuprenorphine, an active metabolite, can further undergo glucuronidation.

Naloxone undergoes direct glucuronidation to naloxone 3-glucuronide as well as N-dealkylation, and reduction of the 6-oxo group.

Elimination:
A mass balance study of buprenorphine showed complete recovery of radiolabel in urine (30%) and feces (69%) collected up to 11 days after dosing. Almost all of the dose was accounted for in terms of buprenorphine, norbuprenorphine, and two unidentified buprenorphine metabolites. In urine, most of buprenorphine and norbuprenorphine was conjugated (buprenorphine, 1% free and 9.4% conjugated; norbuprenorphine, 2.7% free and 11% conjugated). In feces, almost all of the buprenorphine and norbuprenorphine were free (buprenorphine, 33% free and 5% conjugated; norbuprenorphine, 21% free and 2% conjugated).

Buprenorphine has a mean elimination half-life from plasma of 37 h.

Naloxone has a mean elimination half-life from plasma of 1.1 h.

Special Populations:
Hepatic Disease:
The effect of hepatic impairment on the pharmacokinetics of buprenorphine and naloxone is unknown. Since both drugs are extensively metabolized, the plasma levels will be expected to be higher in patients with moderate and severe hepatic impairment. However, it is not known whether both drugs are affected to the same degree. Therefore, in patients with hepatic impairment dosage should be adjusted and patients should be observed for symptoms of precipitated opioid withdrawal.

Renal Disease:
No differences in buprenorphine pharmacokinetics were observed between 9 dialysis-dependent and 6 normal patients following intravenous administration of 0.3mg buprenorphine.

The effects of renal failure on naloxone pharmacokinetics are unknown.

EXHIBIT B

Appendix 1: Product Information

Drug-drug Interactions:
CYP 3A4 Inhibitors and Inducers: A pharmacokinetic interaction study of ketoconazole (400 mg/day), a potent inhibitor of CYP 3A4, in 12 patients stabilized on SUBOXONE [8mg (n=1) or 12mg (n=5) or 16mg (n=6)] resulted in increases in buprenorphine mean C_{max} values (from 4.3 to 9.8, 6.3 to 14.4 and 9.0 to 17.1) and mean AUC values (from 30.9 to 46.9, 41.9 to 83.2 and 52.3 to 120) respectively. Subjects receiving SUBUTEX or SUBOXONE should be closely monitored and may require dose-reduction if inhibitors of CYP 3A4 such as azole antifungal agents (e.g. ketoconazole), macrolide antibiotics (e.g., erythromycin) and HIV protease inhibitors (e.g. ritonavir, indinavir and saquinavir) are co-administered. The interaction of buprenorphine with CYP 3A4 inducers has not been investigated; therefore it is recommended that patients receiving SUBUTEX or SUBOXONE should be closely monitored if inducers of CYP 3A4 (e.g. phenobarbital, carbamazepine, phenytoin, rifampicin) are co-administered (SEE WARNINGS).

CLINICAL STUDIES
Clinical data on the safety and efficacy of SUBOXONE and SUBUTEX are derived from studies of buprenorphine sublingual tablet formulations, with and without naloxone, and from studies of sublingual administration of a more bioavailable ethanolic solution of buprenorphine.

SUBOXONE tablets have been studied in 575 patients, SUBUTEX tablets in 1834 patients and buprenorphine sublingual solutions in 2470 patients. A total of 1270 females have received buprenorphine in clinical trials. Dosing recommendations are based on data from one trial of both tablet formulations and two trials of the ethanolic solution. All trials used buprenorphine in conjunction with psychosocial counseling as part of a comprehensive addiction treatment program. There have been no clinical studies conducted to assess the efficacy of buprenorphine as the only component of treatment.

In a double blind placebo- and active controlled study, 326 heroin-addicted subjects were randomly assigned to either SUBOXONE 16 mg per day, 16 mg SUBUTEX per day or placebo tablets. For subjects randomized to either active treatment, dosing began with one 8 mg tablet of SUBUTEX on Day 1, followed by 16 mg (two 8 mg tablets) of SUBUTEX on Day 2. On Day 3, those randomized to receive SUBOXONE were switched to the combination tablet. Subjects randomized to placebo received one placebo tablet on Day 1 and two placebo tablets per day thereafter for four weeks. Subjects were seen daily in the clinic (Monday through Friday) for dosing and efficacy assessments. Take-home doses were provided for weekends. Subjects were instructed to hold the medication under the tongue for approximately 5 to 10 minutes until completely dissolved. Subjects received one hour of individual counseling per week and a single session of HIV education. The primary study comparison was to assess the efficacy of SUBUTEX and SUBOXONE individually against placebo. The percentage of thrice-weekly urine samples that were negative for non-study opioids was statistically higher for both SUBUTEX and SUBOXONE, than for placebo.

In a double-blind, double-dummy, parallel-group study comparing buprenorphine ethanolic solution to a full agonist active control, 162 subjects were randomized to receive the ethanolic sublingual solution of buprenorphine at 8 mg/day (a dose which is roughly comparable to a dose of 12 mg/day of SUBUTEX or SUBOXONE), or two relatively low doses of active control, one of which was low enough to serve as an alternative to placebo, during a 3-10 day induction phase, a 16-week maintenance phase and a 7-week detoxification phase. Buprenorphine was titrated to maintenance dose by Day 3; active control doses were titrated more gradually.

Maintenance dosing continued through Week 17, and then medications were tapered by approximately 20-30% per week over Weeks 18-24, with placebo dosing for the last two weeks. Subjects received individual and/or group counseling weekly.

Based on retention in treatment and the percentage of thrice-weekly urine samples negative for non-study opioids, buprenorphine was more effective than the low dose of the control, in keeping heroin addicts in treatment and in reducing their use of opioids while in treatment. The effectiveness of buprenorphine, 8 mg per day was similar to that of the moderate active control dose, but equivalence was not demonstrated.

In a dose-controlled, double-blind, parallel-group, 16-week study, 731 subjects were randomized to receive one of four doses of buprenorphine ethanolic solution. Buprenorphine was titrated to maintenance doses over 1-4 days (Table 2) and continued for 16 weeks. Subjects received at least one session of AIDS education and additional counseling ranging from one hour per month to one hour per week, depending on site.

Table 2. Doses of Sublingual Buprenorphine Solution used for Induction in a Double-Blind Dose Ranging Study

Target dose of Buprenorphine *	Induction Dose			Maintenance dose
	Day 1	Day 2	Day 3	
1 mg	1 mg	1 mg	1 mg	1 mg
4 mg	2 mg	4 mg	4 mg	4 mg
8 mg	2 mg	4 mg	8 mg	8 mg
16 mg	2 mg	4 mg	8 mg	16 mg

*Sublingual solution. Doses in this table cannot necessarily be delivered in tablet form, but for comparison purposes:
2 mg solution would be roughly equivalent to 3 mg tablet
4 mg solution would be roughly equivalent to 6 mg tablet
8 mg solution would be roughly equivalent to 12 mg tablet
16 mg solution would be roughly equivalent to 24 mg tablet

Based on retention in treatment and the percentage of thrice-weekly urine samples negative for non-study opioids, the three highest tested doses were superior to the 1mg dose. Therefore, this study showed that a range of buprenorphine doses may be effective. The 1mg dose of buprenorphine sublingual solution can be considered to be somewhat lower than a 2 mg tablet dose. The other doses used in the study encompass a range of tablet doses from approximately 6 mg to approximately 24 mg.

INDICATIONS AND USAGE
SUBOXONE and SUBUTEX are indicated for the treatment of opioid dependence.

CONTRAINDICATIONS
SUBOXONE and SUBUTEX should not be administered to patients who have been shown to be hypersensitive to buprenorphine, and SUBOXONE should not be administered to patients who have been shown to be hypersensitive to naloxone.

WARNINGS
Respiratory Depression:
Significant respiratory depression has been associated with buprenorphine, particularly by the intravenous route. A number of deaths have occurred when addicts have intravenously misused buprenorphine, usually with benzodiazepines concomitantly. Deaths have also been reported in association with concomitant administration of buprenorphine with other depressants such as alcohol or other opioids. Patients should be warned of the potential danger of the self-administration of benzodiazepines or other depressants while under treatment with SUBUTEX or SUBOXONE.

IN THE CASE OF OVERDOSE, THE PRIMARY MANAGEMENT SHOULD BE THE RE-ESTABLISHMENT OF ADEQUATE VENTILATION WITH MECHANICAL ASSISTANCE OF RESPIRATION, IF REQUIRED. NALOXONE MAY NOT BE EFFECTIVE IN REVERSING ANY RESPIRATORY DEPRESSION PRODUCED BY BUPRENORPHINE.

SUBOXONE and SUBUTEX should be used with caution in patients with compromised respiratory function (e.g., chronic obstructive pulmonary disease, cor pulmonale, decreased respiratory reserve, hypoxia, hypercapnia, or pre-existing respiratory depression).

CNS Depression:
Patients receiving buprenorphine in the presence of other narcotic analgesics, general anesthetics, benzodiazepines, phenothiazines, other tranquilizers, sedative/hypnotics or other CNS depressants (including alcohol) may exhibit increased CNS depression. When such combined therapy is contemplated, reduction of the dose of one or both agents should be considered.

Dependence:
Buprenorphine is a partial agonist at the mu-opiate receptor and chronic administration produces dependence of the opioid type, characterized by withdrawal upon abrupt discontinuation or rapid taper. The withdrawal syndrome is milder than seen with full agonists, and may be delayed in onset.

Hepatitis, hepatic events:
Cases of cytolytic hepatitis and hepatitis with jaundice have been observed in the addict population receiving buprenorphine both in clinical trials and in post-marketing adverse event reports. The spectrum of abnormalities ranges from transient asymptomatic elevations in hepatic transaminases to case reports of hepatic failure, hepatic necrosis, hepatorenal syndrome, and hepatic encephalopathy. In many cases, the presence of pre-existing liver enzyme abnormalities, infection with hepatitis B or hepatitis C virus, concomitant usage of other potentially hepatotoxic drugs, and ongoing injecting drug use may have played a causative or contributory role. In other cases, insufficient data were available to determine the etiology of the abnormality. The possibility exists that buprenorphine had a causative or contributory role in the development of the hepatic abnormality in some cases. Measurements of liver function tests prior to initiation of treatment is recommended to establish a baseline. Periodic monitoring of liver function tests during treatment is also recommended. A biological and etiological evaluation is recommended when a hepatic event is suspected. Depending on the case, the drug should be carefully discontinued to prevent withdrawal symptoms and a return to illicit drug use, and strict monitoring of the patient should be initiated.

Allergic Reactions:
Cases of acute and chronic hypersensitivity to buprenorphine have been reported both in clinical trials and in the post-marketing experience. The most common signs and symptoms include rashes, hives, and pruritus. Cases of bronchospasm, angioneurotic edema, and anaphylactic shock have been reported. A history of hypersensitivity to buprenorphine is a contraindication to Subutex or Suboxone use. A history of hypersensitivity to naloxone is a contraindication to Suboxone use.

Use in Ambulatory Patients:
SUBOXONE and SUBUTEX may impair the mental or physical abilities required for the performance of potentially dangerous tasks such as driving a car or operating machinery, especially during drug induction and dose adjustment. Patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that buprenorphine therapy does not adversely affect their ability to engage in such activities. Like other opioids, SUBOXONE and SUBUTEX may produce orthostatic hypotension in ambulatory patients.

Head Injury and Increased Intracranial Pressure:
SUBOXONE and SUBUTEX, like other potent opioids, may elevate cerebrospinal fluid pressure and should be used with caution in patients with head injury, intracranial lesions and other circumstances where cerebrospinal pressure may be increased. SUBOXONE and SUBUTEX can produce miosis and changes in the level of consciousness that may interfere with patient evaluation.

Opioid withdrawal effects:
Because it contains naloxone, SUBOXONE is highly likely to produce marked and intense withdrawal symptoms if misused parenterally by individuals dependent on opioid agonists such as heroin, morphine, or methadone. Sublingually, SUBOXONE may cause opioid withdrawal symptoms in such persons if administered before the agonist effects of the opioid have subsided.

PRECAUTIONS
General:
SUBOXONE and SUBUTEX should be administered with caution in elderly or debilitated patients and those with severe impairment of hepatic, pulmonary, or renal function; myxedema or hypothyroidism, adrenal cortical insufficiency (e.g., Addison's disease); CNS depression or coma; toxic psychoses; prostatic hypertrophy or urethral stricture; acute alcoholism; delirium tremens; or kyphoscoliosis.

The effect of hepatic impairment on the pharmacokinetics of buprenorphine and naloxone is unknown. Since both drugs are extensively metabolized, the plasma levels will be expected to be higher in patients with moderate and severe hepatic impairment. However, it is not known whether both drugs are affected to the same degree. Therefore, dosage should be adjusted and patients should be watched for symptoms of precipitated opioid withdrawal.

Buprenorphine has been shown to increase intracholedochal pressure, as do other opioids, and thus should be administered with caution to patients with dysfunction of the biliary tract.

As with other mu-opioid receptor agonists, the administration of SUBOXONE or SUBUTEX may obscure the diagnosis or clinical course of patients with acute abdominal conditions.

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EXHIBIT B

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Drug Interactions:
Buprenorphine is metabolized to norbuprenorphine by cytochrome CYP 3A4. Because CYP 3A4 inhibitors may increase plasma concentrations of buprenorphine, patients already on CYP 3A4 inhibitors such as azole antifungals (e.g. ketoconazole), macrolide antibiotics (e.g. erythromycin), and HIV protease inhibitors (e.g. ritonavir, indinavir and saquinavir) should have their dose of SUBUTEX or SUBOXONE adjusted.

Based on anecdotal reports, there may be an interaction between buprenorphine and benzodiazepines. There have been a number of reports in the post-marketing experience of coma and death associated with the concomitant intravenous misuse of buprenorphine and benzodiazepines by addicts. In many of these cases, buprenorphine was misused by self-injection of crushed SUBUTEX tablets. SUBUTEX and SUBOXONE should be prescribed with caution to patients on benzodiazepines or other drugs that act on the central nervous system, regardless of whether these drugs are taken on the advice of a physician or are taken as drugs of abuse. Patients should be warned of the potential danger of the intravenous self-administration of benzodiazepines while under treatment with SUBOXONE or SUBUTEX.

Information for Patients:
Patients should inform their family members that, in the event of emergency, the treating physician or emergency room staff should be informed that the patient is physically dependent on narcotics and that the patient is being treated with SUBOXONE or SUBUTEX.

Patients should be cautioned that a serious overdose and death may occur if benzodiazepines, sedatives, tranquilizers, antidepressants, or alcohol are taken at the same time as SUBOXONE or SUBUTEX.

SUBOXONE and SUBUTEX may impair the mental or physical abilities required for the performance of potentially dangerous tasks such as driving a car or operating machinery, especially during drug induction and dose adjustment. Patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that buprenorphine therapy does not adversely affect their ability to engage in such activities. Like other opioids, SUBOXONE and SUBUTEX may produce orthostatic hypotension in ambulatory patients.

Patients should consult their physician if other prescription medications are currently being used or are prescribed for future use.

Carcinogenesis, Mutagenesis and Impairment of Fertility:
Carcinogenicity: Carcinogenicity data on SUBOXONE are not available. Carcinogenicity studies of buprenorphine were conducted in Sprague-Dawley rats and CD-1 mice. Buprenorphine was administered in the diet to rats at doses of 0.6, 5.5, and 56 mg/kg/day (estimated exposure was approximately 0.4, 3 and 35 times the recommended human daily sublingual dose of 16 mg on a mg/m² basis) for 27 months. Statistically significant dose-related increases in testicular interstitial (Leydig's) cell tumors occurred, according to the trend test adjusted for survival. Pair-wise comparison of the high dose against control failed to show statistical significance. In an 86-week study in CD-1 mice, buprenorphine was not carcinogenic at dietary doses up to 100 mg/kg/day (estimated exposure was approximately 30 times the recommended human daily sublingual dose of 16 mg on a mg/m² basis).

Mutagenicity:
SUBOXONE: The 4:1 combination of buprenorphine and naloxone was not mutagenic in a bacterial mutation assay (Ames test) using four strains of *S. typhimurium* and two strains of *E. coli*. The combination was not clastogenic in an *in vitro* cytogenetic assay in human lymphocytes, or in an intravenous micronucleus test in the rat.

SUBUTEX: Buprenorphine was studied in a series of tests utilizing gene, chromosome, and DNA interactions in both prokaryotic and eukaryotic systems. Results were negative in yeast *(Saccharomyces cerevisiae)* for recombinant, gene convertant, or forward mutations; negative in *Bacillus subtilis* "rec" assay, negative for clastogenicity in CHO cells, Chinese hamster bone marrow and spermatogonia cells, and negative in the mouse lymphoma L5178Y assay. Results were equivocal in the Ames test: negative in studies in two laboratories, but positive for frame shift mutation at a high dose (5mg/plate) in a third study. Results were positive in the Green-Tweets *(E. coli)* survival test, positive in a DNA synthesis inhibition (DSI) test with testicular tissue from mice, for both *in vivo* and *in vitro* incorporation of [³H]thymidine, and positive in unscheduled DNA synthesis (UDS) test using testicular cells from mice.

Impairment of Fertility:
SUBOXONE: Dietary administration of SUBOXONE in the rat at dose levels of 500 ppm or greater (equivalent to approximately 47 mg/kg/day or greater; estimated exposure was approximately 28 times the recommended human daily sublingual dose of 16 mg on a mg/m² basis) produced a reduction in fertility demonstrated by reduced female conception rates. A dietary dose of 100 ppm (equivalent to approximately 10 mg/kg/day; estimated exposure was approximately 6 times the recommended human daily sublingual dose of 16 mg on a mg/m² basis) had no adverse effect on fertility.

SUBUTEX: Reproduction studies of buprenorphine in rats demonstrated no evidence of impaired fertility at daily oral doses up to 80mg/kg/day (estimated exposure was approximately 50 times the recommended human daily sublingual dose of 16 mg on a mg/m² basis) or up to 5mg/kg/day *im* or *sc* (estimated exposure was approximately 3 times the recommended human daily sublingual dose of 16 mg on a mg/m² basis).

Pregnancy:
Pregnancy Category C:
Teratogenic effects:
SUBOXONE: Effects on embryo-fetal development were studied in Sprague-Dawley rats and Russian white rabbits following oral (1:1) and intramuscular (3:2) administration of mixtures of buprenorphine and naloxone. Following oral administration to rats and rabbits, no teratogenic effects were observed at doses up to 250 mg/kg/day and 40 mg/kg/day, respectively (estimated exposure was approximately 150 times and 50 times, respectively, the recommended human daily sublingual dose of 16 mg on a mg/m² basis). No definitive drug-related teratogenic effects were observed in rats and rabbits at intramuscular doses up to 30 mg/kg/day (estimated exposure was approximately 20 times and 35 times, respectively, the recommended human daily dose of 16 mg on a mg/m² basis). Acephalus was observed in one rabbit fetus from the low-dose group and omphacele was observed in two rabbit fetuses from the same litter in the mid-dose group; no findings were observed in fetuses from the high-dose group. Following oral administration to the rat, dose-related post-implantation losses, evidenced by increases in the numbers of early resorptions with consequent reductions in the numbers of fetuses, were observed at doses of 10 mg/kg/day or greater (estimated exposure was approximately 6 times the recommended human daily sublingual dose of 16 mg on a mg/m² basis). In the rabbit, increased post-implantation losses occurred at an oral dose of 40 mg/kg/day. Following intramuscular administration in the rat and the rabbit, post-implantation losses, as evidenced by decreases in live fetuses and increases in resorptions, occurred at 30 mg/kg/day.

SUBUTEX: Buprenorphine was not teratogenic in rats or rabbits after *im* or *sc* doses up to 5 mg/kg/day (estimated exposure was approximately 3 and 6 times, respectively, the recommended human daily sublingual dose of 16 mg on a mg/m² basis), after *iv* doses up to 0.8 mg/kg/day (estimated exposure was approximately 0.5 times and equal to, respectively, the recommended human daily sublingual dose of 16 mg on a mg/m² basis), or after oral doses up to 160 mg/kg/day in rats (estimated exposure was approximately 95 times the recommended human daily sublingual dose of 16 mg on a mg/m² basis) and 25 mg/kg/day in rabbits (estimated exposure was approximately 30 times the recommended human daily sublingual dose of 16 mg on a mg/m² basis). Significant increases in skeletal abnormalities (e.g., extra thoracic vertebra or thoraco-lumbar ribs) were noted in rats after *sc* administration of 1 mg/kg/day and up (estimated exposure was approximately 0.6 times the recommended human daily sublingual dose of 16 mg on a mg/m² basis), but were not observed at oral doses up to 160 mg/kg/day. Increases in skeletal abnormalities in rabbits after *im* administration of 5 mg/kg/day (estimated exposure was approximately 6 times the recommended human daily sublingual dose of 16 mg on a mg/m² basis) or oral administration of 1 mg/kg/day or greater (estimated exposure was approximately equal to the recommended human daily sublingual dose of 16 mg on a mg/m² basis) were not statistically significant.

In rabbits, buprenorphine produced statistically significant pre-implantation losses at oral doses of 1 mg/kg/day or greater and post-implantation losses that were statistically significant at *iv* doses of 0.2 mg/kg/day or greater (estimated exposure was approximately 0.3 times the recommended human daily sublingual dose of 16 mg on a mg/m² basis).

There are no adequate and well-controlled studies of SUBOXONE or SUBUTEX in pregnant women. SUBOXONE or SUBUTEX should only be used during pregnancy if the potential benefit justifies the potential risk to the fetus.

Non-teratogenic effects.
Dystocia was noted in pregnant rats treated *im* with buprenorphine 5 mg/kg/day (approximately 3 times the recommended human daily sublingual dose of 16 mg on a mg/m² basis). Both fertility and peri- and postnatal development studies with buprenorphine in rats indicated increases in neonatal mortality after oral doses of 0.8 mg/kg/day and up (approximately 0.5 times the recommended human daily sublingual dose of 16 mg on a mg/m² basis), after *im* doses of 0.5 mg/kg/day and up (approximately 0.3 times the recommended human daily sublingual dose of 16 mg on a mg/m² basis), and after *sc* doses of 0.1 mg/kg/day and up (approximately 0.06 times the recommended human daily sublingual dose of 16 mg on a mg/m² basis). Delays in the occurrence of righting reflex and startle response were noted in rat pups at an oral dose of 80 mg/kg/day (approximately 50 times the recommended human daily sublingual dose of 16 mg on a mg/m² basis).

Neonatal Withdrawal:
Neonatal withdrawal has been reported in the infants of women treated with SUBUTEX during pregnancy. From post-marketing reports, the time to onset of neonatal withdrawal symptoms ranged from Day 1 to Day 8 of life with most occurring on Day 1. Adverse events associated with neonatal withdrawal syndrome included hypertonia, neonatal tremor, neonatal agitation, and myoclonus. There have been rare reports of convulsions and in one case, apnea and bradycardia were also reported.

Nursing Mothers:
An apparent lack of milk production during general reproduction studies with buprenorphine in rats caused decreased viability and lactation indices. Use of high doses of sublingual buprenorphine in pregnant women showed that buprenorphine passes into the mother's milk. Breast-feeding is therefore not advised in mothers treated with SUBUTEX or SUBOXONE.

Pediatric Use:
SUBOXONE and SUBUTEX are not recommended for use in pediatric patients. The safety and effectiveness of SUBOXONE and SUBUTEX in patients below the age of 16 have not been established.

ADVERSE REACTIONS
The safety of SUBOXONE has been evaluated in 497 opioid-dependent subjects. The prospective evaluation of SUBOXONE was supported by clinical trials using SUBUTEX (buprenorphine tablets without naloxone) and other trials using buprenorphine sublingual solutions. In total, safety data are available from 3214 opioid-dependent subjects exposed to buprenorphine at doses in the range used in treatment of opioid addiction.

Few differences in adverse event profile were noted between SUBOXONE and SUBUTEX or buprenorphine administered as a sublingual solution.

In a comparative study, adverse event profiles were similar for subjects treated with 16 mg SUBOXONE or 16mg SUBUTEX. The following adverse events were reported to occur by at least 5% of patients in a 4-week study (Table 3).

Table 3. Adverse Events (≥5%) by Body System and Treatment Group in a 4-week Study

Body System / Adverse Event (COSTART Terminology)	N(%) SUBOXONE 16mg/day N=107	N(%) SUBUTEX 16mg/day N=103	N(%) Placebo N=107
Body as a Whole			
Asthenia	7 (6.5%)	5 (4.9%)	7 (6.5%)
Chills	8 (7.5%)	8 (7.8%)	8 (7.5%)
Headache	39 (36.4%)	30 (29.1%)	24 (22.4%)
Infection	6 (5.6%)	12 (11.7%)	7 (6.5%)
Pain	24 (22.4%)	19 (18.4%)	20 (18.7%)
Pain Abdomen	12 (11.2%)	12 (11.7%)	7 (6.5%)
Pain Back	4 (3.7%)	8 (7.8%)	12 (11.2%)
Withdrawal Syndrome	27 (25.2%)	19 (18.4%)	40 (37.4%)
Cardiovascular System			
Vasodilation	10 (9.3%)	4 (3.9%)	7 (6.5%)
Digestive System			
Constipation	13 (12.1%)	8 (7.8%)	3 (2.8%)
Diarrhea	4 (3.7%)	5 (4.9%)	16 (15.0%)
Nausea	16 (15.0%)	14 (13.6%)	12 (11.2%)
Vomiting	8 (7.5%)	8 (7.8%)	5 (4.7%)
Nervous System			
Insomnia	15 (14.0%)	22 (21.4%)	17 (15.9%)
Respiratory System			
Rhinitis	5 (4.7%)	10 (9.7%)	14 (13.1%)
Skin And Appendages			
Sweating	15 (14.0%)	13 (12.6%)	11 (10.3%)

EXHIBIT B

Appendix 1: Product Information

The adverse event profile of buprenorphine was also characterized in the dose-controlled study of buprenorphine solution, over a range of doses in four months of treatment. Table 4 shows adverse events reported by at least 5% of subjects in any dose group in the dose-controled study.

Table 4. Adverse Events (≥5%) by Body System and Treatment Group in a 16-week Study

Body System / Adverse Event (COSTART Terminology)	Buprenorphine Dose*				
	Very Low* (N=184)	Low* (N=180)	Moderate* (N=186)	High* (N=181)	Total* (N=731)
	N (%)	N (%)	N (%)	N (%)	N (%)
Body as a Whole					
Abscess	9 (5%)	2 (1%)	3 (2%)	2 (1%)	16 (2%)
Asthenia	26 (14%)	28 (16%)	26 (14%)	24 (13%)	104 (14%)
Chills	11 (6%)	12 (7%)	9 (5%)	10 (6%)	42 (6%)
Fever	7 (4%)	2 (1%)	2 (1%)	10 (6%)	21 (3%)
Flu Syndrome	4 (2%)	13 (7%)	19 (10%)	8 (4%)	44 (6%)
Headache	51 (28%)	62 (34%)	54 (29%)	53 (29%)	220 (30%)
Infection	32 (17%)	39 (22%)	38 (20%)	40 (22%)	149 (20%)
Injury Accidental	5 (3%)	10 (6%)	5 (3%)	5 (3%)	25 (3%)
Pain	47 (26%)	37 (21%)	49 (26%)	44 (24%)	177 (24%)
Pain Back	18 (10%)	29 (16%)	28 (15%)	27 (15%)	102 (14%)
Withdrawal Syndrome	45 (24%)	40 (22%)	41 (22%)	36 (20%)	162 (22%)
Digestive System					
Constipation	10 (5%)	23 (13%)	23 (12%)	26 (14%)	82 (11%)
Diarrhea	19 (10%)	8 (4%)	9 (5%)	4 (2%)	40 (5%)
Dyspepsia	6 (3%)	10 (6%)	4 (2%)	4 (2%)	24 (3%)
Nausea	12 (7%)	22 (12%)	23 (12%)	18 (10%)	75 (10%)
Vomiting	8 (4%)	6 (3%)	10 (5%)	14 (8%)	38 (5%)
Nervous System					
Anxiety	22 (12%)	24 (13%)	20 (11%)	25 (14%)	91 (12%)
Depression	24 (13%)	16 (9%)	25 (13%)	18 (10%)	83 (11%)
Dizziness	4 (2%)	9 (5%)	7 (4%)	11 (6%)	31 (4%)
Insomnia	42 (23%)	50 (28%)	43 (23%)	51 (28%)	186 (25%)
Nervousness	12 (7%)	11 (6%)	10 (5%)	13 (7%)	46 (6%)
Somnolence	5 (3%)	13 (7%)	9 (5%)	11 (6%)	38 (5%)
Respiratory System					
Cough Increase	5 (3%)	11 (6%)	6 (3%)	4 (2%)	26 (4%)
Pharyngitis	6 (3%)	7 (4%)	6 (3%)	9 (5%)	28 (4%)
Rhinitis	27 (15%)	16 (9%)	15 (8%)	21 (12%)	79 (11%)
Skin And Appendages					
Sweat	23 (13%)	21 (12%)	20 (11%)	23 (13%)	87 (12%)
Special Senses					
Runny Eyes	13 (7%)	9 (5%)	6 (3%)	6 (3%)	34 (5%)

*Sublingual solution. Doses in this table cannot necessarily be delivered in tablet form, but for comparison purposes:
"Very low" dose (1mg solution) would be less than a tablet dose of 2 mg
"Low" dose (4mg solution) approximates a 6 mg tablet dose
"Moderate" dose (8mg solution) approximates a 12 mg tablet dose
"High" dose (16mg solution) approximates a 24 mg tablet dose

DRUG ABUSE AND DEPENDENCE
SUBOXONE and SUBUTEX are controlled as Schedule III narcotics under the Controlled Substances Act.

Buprenorphine is a partial agonist at the mu-opioid receptor and chronic administration produces dependence of the opioid type, characterized by moderate withdrawal upon abrupt discontinuation or rapid taper. The withdrawal syndrome is milder than seen with full agonists, and may be delayed in onset (SEE WARNINGS)

Neonatal withdrawal has been reported in the infants of women treated with SUBUTEX during pregnancy (See PRECAUTIONS)

SUBOXONE contains naloxone and if misused parenterally, is highly likely to produce marked and intense withdrawal symptoms in subjects dependent on other opioid agonists.

OVERDOSAGE
Manifestations:
Manifestations of acute overdose include pinpoint pupils, sedation, hypotension, respiratory depression and death.

Treatment:
The respiratory and cardiac status of the patient should be monitored carefully. In the event of depression of respiratory or cardiac function, primary attention should be given to the re-establishment of adequate respiratory exchange through provision of a patent airway and institution of assisted or controlled ventilation. Oxygen, intravenous fluids, vasopressors, and other supportive measures should be employed as indicated.

IN THE CASE OF OVERDOSE, THE PRIMARY MANAGEMENT SHOULD BE THE RE-ESTABLISHMENT OF ADEQUATE VENTILATION WITH MECHANICAL ASSISTANCE OF RESPIRATION, IF REQUIRED. NALOXONE MAY NOT BE EFFECTIVE IN REVERSING ANY RESPIRATORY DEPRESSION PRODUCED BY BUPRENORPHINE.

High doses of naloxone hydrochloride, 10-35 mg/70 kg may be of limited value in the management of buprenorphine overdose. Doxapram (a respiratory stimulant) also has been used.

DOSAGE AND ADMINISTRATION
SUBUTEX or SUBOXONE is administered sublingually as a single daily dose in the range of 12 to 16mg/day. When taken sublingually, SUBOXONE and SUBUTEX have similar clinical effects and are interchangeable. There are no adequate and well-controlled studies using SUBOXONE as initial medication. SUBUTEX contains no naloxone and is preferred for use during induction. Following induction, SUBOXONE, due to the presence of naloxone, is preferred when clinical use includes unsupervised administration. The use of SUBUTEX for unsupervised administration should be limited to those patients who cannot tolerate SUBOXONE, for example those patients who have been shown to be hypersensitive to naloxone.

Method of administration:
SUBOXONE and SUBUTEX tablets should be placed under the tongue until they are dissolved.
For doses requiring the use of more than two tablets, patients are advised to either place all the tablets at once or alternatively (if they cannot fit in more than two tablets comfortably) place two tablets at a time under the tongue. Either way, the patients should continue to hold the tablets under the tongue until they dissolve; swallowing the tablets reduces the bioavailability of the drug. To ensure consistency in bioavailability, patients should follow the same manner of dosing with continued use of the product.

Induction:
Prior to induction, consideration should be given to the type of opioid dependence (i.e. long- or short-acting opioid), the time since last opioid use, and the degree or level of opioid dependence. To avoid precipitating withdrawal, induction with SUBUTEX should be undertaken when objective and clear signs of withdrawal are evident.

In a one-month study of SUBOXONE tablets induction was conducted with SUBUTEX tablets. Patients received 8mg of SUBUTEX on day 1 and 16mg SUBUTEX on day 2. From day 3 onward, patients received SUBOXONE tablets at the same buprenorphine dose as day 2. Induction in the studies of buprenorphine solution was accomplished over 3-4 days, depending on the target dose.
In some studies, gradual induction over several days led to a high rate of drop-out of buprenorphine patients during the induction period. Therefore it is recommended that an adequate maintenance dose, titrated to clinical effectiveness, should be achieved as rapidly as possible to prevent undue opioid withdrawal symptoms.

Patients taking heroin or other short-acting opioids:
At treatment initiation, the dose of SUBUTEX should be administered at least 4 hours after the patient last used opioids or preferably when early signs of opioid withdrawal appear.

Patients on methadone or other long-acting opioids:
There is little controlled experience with the transfer of methadone-maintained patients to buprenorphine. Available evidence suggests that withdrawal symptoms are possible during induction to buprenorphine treatment. Withdrawal appears more likely in patients maintained on higher doses of methadone (>30mg) and when the first buprenorphine dose is administered shortly after the last methadone dose.

Maintenance:
SUBOXONE is the preferred medication for maintenance treatment due to the presence of naloxone in the formulation.

Adjusting the dose until the maintenance dose is achieved:
The recommended target dose of SUBOXONE is 16 mg/day. Clinical studies have shown that 16mg of SUBUTEX or SUBOXONE is a clinically effective dose compared with placebo and indicate that doses as low as 12 mg may be effective in some patients. The dosage of SUBOXONE should be progressively adjusted in increments / decrements of 2mg or 4mg to a level that holds the patient in treatment and suppresses opioid withdrawal effects. This is likely to be in the range of 4mg to 24mg per day depending on the individual.

Reducing dosage and stopping treatment:
The decision to discontinue therapy with SUBOXONE or SUBUTEX after a period of maintenance or brief stabilization should be made as part of a comprehensive treatment plan. Both gradual and abrupt discontinuation have been used, but no controlled trials have been undertaken to determine the best method of dose taper at the end of treatment.

HOW SUPPLIED
SUBOXONE is supplied as sublingual tablets in white HDPE bottles.

Hexagonal orange tablets containing 2mg buprenorphine with 0.5mg naloxone
NDC 12496-1283-2 30 tablets per bottle

Hexagonal orange tablets containing 8mg buprenorphine with 2mg naloxone

NDC 12496-1306-2 30 tablets per bottle

Store at 25°C (77°F), excursions permitted to 15-30°C
(59-86°F) [see USP Controlled Room Temperature]

SUBUTEX is supplied as sublingual tablets in white HDPE bottles.

Oval white tablets containing 2mg buprenorphine
NDC 12496-1278-2 30 tablets per bottle

Oval white tablets containing 8mg buprenorphine
NDC 12496-1310-2 30 tablets per bottle

Store at 25°C (77°F), excursions permitted to 15-30°C
(59-86°F) [see USP Controlled Room Temperature]

Manufactured by:
Reckitt Benckiser Healthcare (UK) Ltd
Hull, UK, HU8 7DS

Distributed by:
Reckitt Benckiser Pharmaceuticals, Inc.
Richmond, VA 23235

Last revised June 2005

#0044284

EXHIBIT C

Reckitt Benckiser Pharmaceuticals Inc.

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use SUBOXONE® sublingual film safely and effectively. See full prescribing information for SUBOXONE sublingual film.

SUBOXONE (buprenorphine and naloxone) sublingual film for sublingual administration CIII.

Initial U.S. Approval: 2002

----------INDICATIONS AND USAGE----------

SUBOXONE sublingual film is indicated for maintenance treatment of opioid dependence. Prescription use of this product is limited under the Drug Addiction Treatment Act. (1)

----------DOSAGE AND ADMINISTRATION----------

Administer SUBOXONE sublingual film sublingually as a single daily dose. (2)

The recommended daily dose for maintenance treatment is 16 mg/4 mg buprenorphine and naloxone. Advise patients not to cut, chew, or swallow SUBOXONE sublingual film.

----------DOSAGE FORMS AND STRENGTHS----------

Sublingual film: 2 mg buprenorphine with 0.5 mg naloxone, 4 mg buprenorphine with 1 mg naloxone, 8 mg buprenorphine with 2 mg naloxone, and 12 mg buprenorphine with 3 mg naloxone. (3)

----------CONTRAINDICATIONS----------

Hypersensitivity to buprenorphine or naloxone. (4)

----------WARNINGS AND PRECAUTIONS----------

- Buprenorphine can be abused in a similar manner to other opioids. Clinical monitoring appropriate to the patient's level of stability is essential. Multiple refills should not be prescribed early in treatment or without appropriate patient follow-up visits. (5.1)
- Significant respiratory depression and death have occurred in association with buprenorphine, particularly when taken by the intravenous (IV) route in combination with benzodiazepines or other CNS depressants (including alcohol). (5.2)
- Consider dose reduction of CNS depressants, SUBOXONE sublingual film, or both in situations of concomitant prescription. (5.3)
- Store SUBOXONE sublingual film safely out of the sight and reach of children. Buprenorphine can cause severe, possibly fatal, respiratory depression in children. (5.4)
- Chronic administration produces opioid-type physical dependence. Abrupt discontinuation or rapid dose taper may result in opioid withdrawal syndrome. (5.5)
- Monitor liver function tests prior to initiation and during treatment and evaluate suspected hepatic events. (5.6)
- Do not administer SUBOXONE sublingual film to patients with known hypersensitivity to buprenorphine or naloxone. (5.7)
- A marked and intense opioid withdrawal syndrome is highly likely to occur with parenteral misuse of SUBOXONE sublingual film by individuals physically dependent on full opioid agonists or by sublingual administration before the agonist effects of other opioids have subsided. (5.8)
- Neonatal withdrawal has been reported following use of buprenorphine by the mother during pregnancy. (5.9)
- SUBOXONE sublingual film is not appropriate as an analgesic. There have been reported deaths of opioid naïve individuals who received a 2 mg sublingual dose. (5.10)
- Caution patients about the risk of driving or operating hazardous machinery. (5.11)

----------ADVERSE REACTIONS----------

Adverse events commonly observed with the sublingual administration of the SUBOXONE sublingual film was oral hypoesthesia, glossodynia, oral mucosal erythema, headache, nausea, vomiting, hyperhidrosis, constipation, signs and symptoms of withdrawal, insomnia, pain, and peripheral edema. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Reckitt Benckiser Pharmaceuticals Inc. at 1-877-782-6966, FDA at 1-800-FDA-1088, or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------

- Monitor patients starting or ending CYP3A4 inhibitors or inducers for potential over or under dosing. (7.1)
- Use caution in prescribing SUBOXONE sublingual film for patients receiving benzodiazepines or other CNS depressants and warn patients against concomitant self-administration/misuse. (7.3)

----------USE IN SPECIFIC POPULATIONS----------

- SUBOXONE sublingual film is not indicated for use during pregnancy unless potential benefit justifies potential risk. (8.1)
- Buprenorphine passes into the mother's milk. Breast-feeding is not advised while taking SUBOXONE sublingual film. (8.3)
- Safety and effectiveness of SUBOXONE sublingual film in patients below the age of 16 has not been established. (8.4)
- Administer SUBOXONE sublingual film with caution to elderly or debilitated patients. (8.5)
- Administer SUBOXONE sublingual film with caution to patients with liver dysfunction. (8.6)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

Approved August 2012

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections and subsections omitted from the full prescribing information are not listed.

EXHIBIT C

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See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

Approved August 2012

ENTS*

ıaloxone) Sublingual Tablets

ublingual Film

EXHIBIT C

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

SUBOXONE sublingual film is indicated for maintenance treatment of opioid dependence and should be used as part of a complete treatment plan to include counseling and psychosocial support.

Under the Drug Addiction Treatment Act (DATA) codified at 21 U.S.C. 823(g), prescription use of this product in the treatment of opioid dependence is limited to physicians who meet certain qualifying requirements, and who have notified the Secretary of Health and Human Services (HHS) of their intent to prescribe this product for the treatment of opioid dependence and have been assigned a unique identification number that must be included on every prescription.

2 DOSAGE AND ADMINISTRATION

SUBOXONE sublingual film is administered sublingually as a single daily dose. SUBOXONE sublingual film should be used in patients who have been initially inducted using buprenorphine sublingual tablets.

2.1 Maintenance

- SUBOXONE sublingual film is indicated for maintenance treatment. The recommended target dosage of SUBOXONE sublingual film is 16 mg/4 mg buprenorphine/naloxone/day as a single daily dose.
- The dosage of SUBOXONE sublingual film should be progressively adjusted in increments/decrements of 2 mg/0.5 mg or 4 mg/1 mg buprenorphine/naloxone to a level that holds the patient in treatment and suppresses opioid withdrawal signs and symptoms.
- The maintenance dose of SUBOXONE sublingual film is generally in the range of 4 mg/1 mg buprenorphine/naloxone to 24 mg/6 mg buprenorphine/naloxone per day depending on the individual patient. Dosages higher than this have not been demonstrated to provide any clinical advantage.

2.2 Method of Administration

Do not cut, chew, or swallow SUBOXONE sublingual film. Place a sublingual film under the tongue. If an additional sublingual film is necessary to achieve the prescribed dose, place an additional sublingual film sublingually on the opposite side from the first film. Place the sublingual film in a manner to minimize overlapping as much as possible. The sublingual film must be kept under the tongue until the film is completely dissolved. **SUBOXONE sublingual film should NOT be moved after placement.**

Proper administration technique should be demonstrated to the patient.

2.3 Clinical Supervision

Treatment should be initiated with supervised administration, progressing to unsupervised administration as the patient's clinical stability permits. SUBOXONE sublingual film is subject to diversion and abuse. When determining the prescription quantity for unsupervised administration, consider the patient's level of stability, the security of his or her home situation, and other factors likely to affect the ability to manage supplies of take-home medication.

Ideally patients should be seen at reasonable intervals (e.g., at least weekly during the first month of treatment) based upon the individual circumstances of the patient. Medication should be prescribed in consideration of the frequency of visits. Provision of multiple refills is not advised early in treatment or without appropriate patient follow-up visits. Periodic assessment is necessary to determine compliance with the dosing regimen, effectiveness of the treatment plan, and overall patient progress.

Once a stable dosage has been achieved and patient assessment (e.g., urine drug screening) does not indicate illicit drug use, less frequent follow-up visits may be appropriate. A once-monthly visit schedule may be reasonable for patients on a stable dosage of medication who are making progress toward their treatment objectives. Continuation or modification of pharmacotherapy should be based on the physician's evaluation of treatment outcomes and objectives such as:

1. Absence of medication toxicity.
2. Absence of medical or behavioral adverse effects.
3. Responsible handling of medications by the patient.
4. Patient's compliance with all elements of the treatment plan (including recovery-oriented activities, psychotherapy, and/or other psychosocial modalities).
5. Abstinence from illicit drug use (including problematic alcohol and/or benzodiazepine use).

If treatment goals are not being achieved, the physician should re-evaluate the appropriateness of continuing the current treatment.

2.4 Unstable Patients

Physicians will need to decide when they cannot appropriately provide further management for particular patients. For example, some patients may be abusing or dependent on various drugs, or unresponsive to psychosocial intervention such that the physician does not feel that he/she has the expertise to manage the patient. In such cases, the physician may want to assess whether to refer the patient to a specialist or more intensive behavioral treatment environment. Decisions should be based on a treatment plan established and agreed upon with the patient at the beginning of treatment.

Patients who continue to misuse, abuse, or divert buprenorphine products or other opioids should be provided with, or referred to, more intensive and structured treatment.

2.5 Stopping Treatment

The decision to discontinue therapy with SUBOXONE sublingual film after a period of maintenance should be made as part of a comprehensive treatment plan. Both gradual and abrupt discontinuation of buprenorphine has been used, but the data are insufficient to determine the best method of dose taper at the end of treatment.

2.6 Switching between SUBOXONE Sublingual Tablets and SUBOXONE Sublingual Film

Patients being switched between SUBOXONE sublingual tablets and SUBOXONE sublingual film should be started on the same dosage as the previously administered product. However, dosage adjustments may be necessary when switching between products. Not all strengths and combinations of the SUBOXONE sublingual films are bioequivalent to the SUBOXONE sublingual tablets as observed in pharmacokinetic studies *[see Clinical Pharmacology (12.3)]*. Therefore, systemic exposures of buprenorphine and naloxone may be different when patients are switched from tablets to strips or vice-versa. Patients should be monitored for symptoms related to over-dosing or under-dosing.

2.7 Switching between SUBOXONE Sublingual Film strengths

As indicated in Table 1, the sizes and the compositions of the four units of SUBOXONE sublingual films, i.e., 2 mg/0.5 mg, 4 mg/1 mg, 8 mg/2 mg and the 12 mg/3 mg units, are different from one another. If patients switch between various combinations of lower and higher strength units of SUBOXONE sublingual films to obtain the same total dose, (e.g., from three 4 mg/1 mg units to a single 12 mg/3 mg unit, or vice-versa), systemic exposures of buprenorphine and naloxone may be different and patients should be monitored for over-dosing or under-dosing. For this reason, pharmacist should not substitute one or more film strengths for another without approval of the prescriber.

Table 1. Comparison of available SUBOXONE film strengths by dimensions and drug concentrations.

SUBOXONE film unit strength (buprenorphine/naloxone)	SUBOXONE film unit dimensions	Buprenorphine Concentration % (w/w)	Naloxone Concentration % (w/w)
2 mg/0.5 mg	22.0 mm x 12.8 mm	5.4	1.53
4 mg/1 mg (2 times the length of the 2 mg/0.5 mg unit)	22.0 mm x 25.6 mm	5.4	1.53
8 mg/2 mg	22.0 mm x 12.8 mm	17.2	4.88
12 mg/3 mg (1.5 times the length of the 8 mg/2 mg unit)	22.0 mm x 19.2 mm	17.2	4.88

3 DOSAGE FORMS AND STRENGTHS

SUBOXONE sublingual film is supplied as an orange rectangular sublingual film with a white printed logo in four dosage strengths:

- buprenorphine/naloxone 2 mg/0.5 mg,
- buprenorphine/naloxone 4 mg/1 mg,
- buprenorphine/naloxone 8 mg/2 mg, and
- buprenorphine/naloxone 12 mg/3 mg

4 CONTRAINDICATIONS

SUBOXONE sublingual film should not be administered to patients who have been shown to be hypersensitive to buprenorphine or naloxone as serious adverse reactions, including anaphylactic shock, have been reported *[see Warnings and Precautions (5.7)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Abuse Potential

Buprenorphine can be abused in a manner similar to other opioids, legal or illicit. Prescribe and dispense buprenorphine with appropriate precautions to minimize risk of misuse, abuse, or diversion, and ensure appropriate protection from theft, including in the home. Clinical monitoring appropriate to the patient's level of stability is essential. Multiple refills should not be prescribed early in treatment or without appropriate patient follow-up visits. *[see Drug Abuse and Dependence (9.2)]*.

5.2 Respiratory Depression

Buprenorphine, particularly when taken by the IV route, in combination with benzodiazepines or other CNS depressants (including alcohol), has been associated with significant respiratory depression and death. Many, but not all, post-marketing reports regarding coma and death associated with the concomitant use of buprenorphine and benzodiazepines involved misuse by self-injection. Deaths have also been reported in association with concomitant administration of buprenorphine with other depressants such as alcohol or other CNS depressant drugs. Patients should be warned of the potential danger of self-administration of benzodiazepines or other depressants while under treatment with SUBOXONE sublingual film. [see *Drug Interactions* (7.3)].

In the case of overdose, the primary management should be the re-establishment of adequate ventilation with mechanical assistance of respiration, if required. Naloxone may be of value for the management of buprenorphine overdose. Higher than normal doses and repeated administration may be necessary.

SUBOXONE sublingual film should be used with caution in patients with compromised respiratory function (e.g., chronic obstructive pulmonary disease, cor pulmonale, decreased respiratory reserve, hypoxia, hypercapnia, or pre-existing respiratory depression).

5.3 CNS Depression

Patients receiving buprenorphine in the presence of opioid analgesics, general anesthetics, benzodiazepines, phenothiazines, other tranquilizers, sedative/hypnotics, or other CNS depressants (including alcohol) may exhibit increased CNS depression. Consider dose reduction of CNS depressants, SUBOXONE sublingual film, or both in situations of concomitant prescription. *[see Drug Interactions (7.3)]*.

5.4 Unintentional Pediatric Exposure

Buprenorphine can cause severe, possibly fatal, respiratory depression in children who are accidentally exposed to it. Store buprenorphine-containing medications safely out of the sight and reach of children.

EXHIBIT C

5.5 Dependence

Buprenorphine is a partial agonist at the mu-opioid receptor and chronic administration produces physical dependence of the opioid type, characterized by withdrawal signs and symptoms upon abrupt discontinuation or rapid taper. The withdrawal syndrome is typically milder than seen with full agonists and may be delayed in onset. Buprenorphine can be abused in a manner similar to other opioids. This should be considered when prescribing or dispensing buprenorphine in situations when the clinician is concerned about an increased risk of misuse, abuse, or diversion. *[see Drug Abuse and Dependence (9.3)]*

5.6 Hepatitis, Hepatic Events

Cases of cytolytic hepatitis and hepatitis with jaundice have been observed in individuals receiving buprenorphine in clinical trials and through post-marketing adverse event reports. The spectrum of abnormalities ranges from transient asymptomatic elevations in hepatic transaminases to case reports of death, hepatic failure, hepatic necrosis, hepatorenal syndrome, and hepatic encephalopathy. In many cases, the presence of pre-existing liver enzyme abnormalities, infection with hepatitis B or hepatitis C virus, concomitant usage of other potentially hepatotoxic drugs, and ongoing injecting drug use may have played a causative or contributory role. In other cases, insufficient data were available to determine the etiology of the abnormality. Withdrawal of buprenorphine has resulted in amelioration of acute hepatitis in some cases; however, in other cases no dose reduction was necessary. The possibility exists that buprenorphine had a causative or contributory role in the development of the hepatic abnormality in some cases. Liver function tests, prior to initiation of treatment is recommended to establish a baseline. Periodic monitoring of liver function during treatment is also recommended. A biological and etiological evaluation is recommended when a hepatic event is suspected. Depending on the case, SUBOXONE sublingual film may need to be carefully discontinued to prevent withdrawal signs and symptoms and a return by the patient to illicit drug use, and strict monitoring of the patient should be initiated.

5.7 Allergic Reactions

Cases of hypersensitivity to buprenorphine and naloxone containing products have been reported both in clinical trials and in the post-marketing experience. Cases of bronchospasm, angioneurotic edema, and anaphylactic shock have been reported. The most common signs and symptoms include rashes, hives, and pruritus. A history of hypersensitivity to buprenorphine or naloxone is a contraindication to the use of SUBOXONE sublingual film.

5.8 Precipitation of Opioid Withdrawal Signs and Symptoms

Because it contains naloxone, SUBOXONE sublingual film is highly likely to produce marked and intense withdrawal signs and symptoms if misused parenterally by individuals dependent on full opioid agonists such as heroin, morphine, or methadone. Because of the partial agonist properties of buprenorphine, SUBOXONE sublingual film may precipitate opioid withdrawal signs and symptoms in such persons if administered sublingually before the agonist effects of the opioid have subsided.

5.9 Neonatal Withdrawal

Neonatal withdrawal has been reported in the infants of women treated with buprenorphine during pregnancy. From post-marketing reports, the time to onset of neonatal withdrawal signs ranged from Day 1 to Day 8 of life with most cases occurring on Day 1. Adverse events associated with the neonatal withdrawal syndrome included hypertonia, neonatal tremor, neonatal agitation, and myoclonus, and there have been reports of convulsions, apnea, respiratory depression, and bradycardia.

5.10 Use in Opioid Naïve Patients

There have been reported deaths of opioid naive individuals who received a 2 mg dose of buprenorphine as a sublingual tablet for analgesia. SUBOXONE sublingual film is not appropriate as an analgesic.

5.11 Impairment of Ability to Drive or Operate Machinery

SUBOXONE sublingual film may impair the mental or physical abilities required for the performance of potentially dangerous tasks such as driving a car or operating machinery, especially during treatment induction and dose adjustment. Patients should be cautioned about driving or operating hazardous machinery until they are reasonably certain that SUBOXONE sublingual film therapy does not adversely affect his or her ability to engage in such activities.

5.12 Orthostatic Hypotension

Like other opioids, SUBOXONE sublingual film may produce orthostatic hypotension in ambulatory patients.

5.13 Elevation of Cerebrospinal Fluid Pressure

Buprenorphine, like other opioids, may elevate cerebrospinal fluid pressure and should be used with caution in patients with head injury, intracranial lesions, and other circumstances when cerebrospinal pressure may be increased. Buprenorphine can produce miosis and changes in the level of consciousness that may interfere with patient evaluation.

5.14 Elevation of Intracholedochal Pressure

Buprenorphine has been shown to increase intracholedochal pressure, as do other opioids, and thus should be administered with caution to patients with dysfunction of the biliary tract.

5.15 Effects in Acute Abdominal Conditions

As with other opioids, buprenorphine may obscure the diagnosis or clinical course of patients with acute abdominal conditions.

5.16 General Precautions

SUBOXONE sublingual film should be administered with caution in debilitated patients and those with myxedema or hypothyroidism, adrenal cortical insufficiency (e.g., Addison's disease); CNS depression or coma; toxic psychoses; prostatic hypertrophy or urethral stricture; acute alcoholism; delirium tremens; or kyphoscoliosis.

6 ADVERSE REACTIONS

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

6.1 Adverse Events in Clinical Trials - SUBOXONE sublingual film

The safety of SUBOXONE sublingual film is supported by clinical trials using SUBUTEX (buprenorphine) sublingual tablets and SUBOXONE (buprenorphine and naloxone) sublingual tablets, and other trials using buprenorphine sublingual solutions, as well as an open-label study in 194 patients treated with SUBOXONE sublingual film. In total, safety data from clinical studies are available from over 3000 opioid-dependent subjects exposed to buprenorphine at doses in the range used in the treatment of opioid dependence. Few differences in the adverse event profile were noted among SUBOXONE sublingual film, SUBOXONE (buprenorphine and naloxone) sublingual tablets, SUBUTEX (buprenorphine) sublingual tablets and a buprenorphine ethanolic sublingual solution.

The most common adverse event (>1%) associated with the sublingual administration of the SUBOXONE sublingual film was oral hypoesthesia. Other adverse events were constipation, glossodynia, oral mucosal erythema, vomiting, intoxication, disturbance in attention, palpitations, insomnia, withdrawal syndrome, hyperhidrosis, and blurred vision.

Other adverse event data were derived from larger, controlled studies of SUBOXONE (buprenorphine and naloxone) and SUBUTEX (buprenorphine) tablets and of buprenorphine sublingual solution. In a comparative study of SUBOXONE (buprenorphine and naloxone) and SUBUTEX (buprenorphine) sublingual tablets, adverse event profiles were similar for subjects treated with 16 mg/4 mg SUBOXONE (buprenorphine and naloxone) sublingual tablets or 16 mg SUBUTEX (buprenorphine) sublingual tablets. The following adverse events were reported to occur by at least 5% of patients in a 4-week study of SUBOXONE (buprenorphine and naloxone) sublingual tablets and SUBUTEX (buprenorphine) sublingual tablets.

Table 2. Adverse Events (≥5%) by Body System and Treatment Group in a 4-week Study

Body System/ Adverse Event (COSTART Terminology)	SUBOXONE (buprenorphine and naloxone) sublingual tablets 16 mg/4 mg/day N=107 n (%)	SUBUTEX (buprenorphine) sublingual tablets 16 mg/day N=103 n (%)	Placebo N=107 n (%)
Body as a Whole			
Asthenia	7 (6.5%)	5 (4.9%)	7 (6.5%)
Chills	8 (7.5%)	8 (7.8%)	8 (7.5%)
Headache	39 (36.4%)	30 (29.1%)	24 (22.4%)
Infection	6 (5.6%)	12 (11.7%)	7 (6.5%)
Pain	24 (22.4%)	19 (18.4%)	20 (18.7%)
Pain abdomen	12 (11.2%)	12 (11.7%)	7 (6.5%)
Pain back	4 (3.7%)	8 (7.8%)	12 (11.2%)
Withdrawal syndrome	27 (25.2%)	19 (18.4%)	40 (37.4%)
Cardiovascular System			
Vasodilation	10 (9.3%)	4 (3.9%)	7 (6.5%)
Digestive System			
Constipation	13 (12.1%)	8 (7.8%)	3 (2.8%)
Diarrhea	4 (3.7%)	5 (4.9%)	16 (15.0%)
Nausea	16 (15.0%)	14 (13.6%)	12 (11.2%)
Vomiting	8 (7.5%)	8 (7.8%)	5 (4.7%)
Nervous System			
Insomnia	15 (14.0%)	22 (21.4%)	17 (15.9%)
Respiratory System			
Rhinitis	5 (4.7%)	10 (9.7%)	14 (13.1%)
Skin And Appendages			
Sweating	15 (14.0%)	13 (12.6%)	11 (10.3%)

Abbreviations: COSTART = Coding Symbols for Thesaurus of Adverse Reaction Terms.

The adverse event profile of buprenorphine was also characterized in the dose-controlled study of a buprenorphine ethanolic solution, over a range of doses in four months of treatment. Table 3 shows adverse events reported by at least 5% of subjects in any dose group in the dose-controlled trial.

Table 3. Adverse Events (≥5%) by Body System and Treatment Group in a 16-week Study

Body System/ Adverse Event (COSTART Terminology)	Buprenorphine Dose				
	Very Low* N=184 n (%)	Low* N=180 n (%)	Moderate* N=186 n (%)	High* N=181 n (%)	Total* N=731 n (%)
Body as a Whole					
Abscess	9 (5%)	2 (1%)	3 (2%)	2 (1%)	16 (2%)
Asthenia	26 (14%)	28 (16%)	26 (14%)	24 (13%)	104 (14%)
Chills	11 (6%)	12 (7%)	9 (5%)	10 (6%)	42 (6%)
Fever	7 (4%)	2 (1%)	2 (1%)	10 (6%)	21 (3%)
Flu syndrome	4 (2%)	13 (7%)	19 (10%)	8 (4%)	44 (6%)
Headache	51 (28%)	62 (34%)	54 (29%)	53 (29%)	220 (30%)
Infection	32 (17%)	39 (22%)	38 (20%)	40 (22%)	149 (20%)
Injury accidental	5 (3%)	10 (6%)	5 (3%)	5 (3%)	25 (3%)
Pain	47 (26%)	37 (21%)	49 (26%)	44 (24%)	177 (24%)
Pain back	18 (10%)	29 (16%)	28 (15%)	27 (15%)	102 (14%)
Withdrawal syndrome	45 (24%)	40 (22%)	41 (22%)	36 (20%)	162 (22%)
Digestive System					
Constipation	10 (5%)	23 (13%)	23 (12%)	26 (14%)	82 (11%)
Diarrhea	19 (10%)	8 (4%)	9 (5%)	4 (2%)	40 (5%)

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Body System/ Adverse Event (COSTART Terminology)	Buprenorphine Dose				
	Very Low* N=184 n (%)	Low* N=180 n (%)	Moderate* N=186 n (%)	High* N=181 n (%)	Total* N=731 n (%)
Dyspepsia	6 (3%)	10 (6%)	4 (2%)	4 (2%)	24 (3%)
Nausea	12 (7%)	22 (12%)	23 (12%)	18 (10%)	75 (10%)
Vomiting	8 (4%)	6 (3%)	10 (5%)	14 (8%)	38 (5%)
Nervous System					
Anxiety	22 (12%)	24 (13%)	20 (11%)	25 (14%)	91 (12%)
Depression	24 (13%)	16 (9%)	25 (13%)	18 (10%)	83 (11%)
Dizziness	4 (2%)	9 (5%)	7 (4%)	11 (6%)	31 (4%)
Insomnia	42 (23%)	50 (28%)	43 (23%)	51 (28%)	186 (25%)
Nervousness	12 (7%)	11 (6%)	10 (5%)	13 (7%)	46 (6%)
Somnolence	5 (3%)	13 (7%)	9 (5%)	11 (6%)	38 (5%)
Respiratory System					
Cough increase	5 (3%)	11 (6%)	6 (3%)	4 (2%)	26 (4%)
Pharyngitis	6 (3%)	7 (4%)	6 (3%)	9 (5%)	28 (4%)
Rhinitis	27 (15%)	16 (9%)	15 (8%)	21 (12%)	79 (11%)
Skin and Appendages					
Sweat	23 (13%)	21 (12%)	20 (11%)	23 (13%)	87 (12%)
Special Senses					
Runny eyes	13 (7%)	9 (5%)	6 (3%)	6 (3%)	34 (5%)

*Sublingual solution. Doses in this table cannot necessarily be delivered in tablet form, but for comparison purposes:

1 mg solution would be less than a tablet dose of 2 mg

4 mg solution approximates a 6 mg tablet dose

8 mg solution approximates a 12 mg tablet dose

16 mg solution approximates a 24 mg tablet dose

6.2 Adverse Events – Post-marketing Experience with SUBOXONE Sublingual Tablets

The most frequently reported post-marketing adverse event not observed in clinical trials was peripheral edema.

7 DRUG INTERACTIONS

7.1 Cytochrome P-450 3A4 (CYP3A4) Inhibitors and Inducers

Buprenorphine is metabolized to norbuprenorphine primarily by cytochrome CYP3A4; therefore, potential interactions may occur when SUBOXONE sublingual film is given concurrently with agents that affect CYP3A4 activity. The concomitant use of SUBOXONE sublingual film with CYP3A4 inhibitors (e.g., azole antifungals such as ketoconazole, macrolide antibiotics such as erythromycin, and HIV protease inhibitors) should be monitored and may require dose-reduction of one or both agents.

The interaction of buprenorphine with CYP3A4 inducers has not been studied; therefore, it is recommended that patients receiving SUBOXONE sublingual film be monitored for signs and symptoms of opioid withdrawal if inducers of CYP3A4 (e.g., efavirenz, phenobarbital, carbamazepine, phenytoin, rifampicin) are co-administered [see Clinical Pharmacology (12.3)].

7.2 Antiretrovirals

Three classes of antiretroviral agents have been evaluated for CYP3A4 interactions with buprenorphine. Nucleoside reverse transcriptase inhibitors (NRTIs) do not appear to induce or inhibit the P450 enzyme pathway, thus no interactions with buprenorphine are expected. Non-nucleoside reverse transcriptase inhibitors (NNRTIs) are metabolized principally by CYP3A4. Efavirenz, nevirapine and etravirine are known CYP3A inducers whereas delavirdine is a CYP3A inhibitor. Significant pharmacokinetic interactions between NNRTIs (e.g., efavirenz and delavirdine) and buprenorphine have been shown in clinical studies, but these pharmacokinetic interactions did not result in any significant pharmacodynamic effects. It is recommended that patients who are on chronic buprenorphine treatment have their dose monitored if NNRTIs are added to their treatment regimen. Studies have shown some antiretroviral protease inhibitors (PIs) with CYP3A4 inhibitory activity (nelfinavir, lopinavir/ritonavir, ritonavir) have little effect on buprenorphine pharmacokinetic and no significant pharmacodynamic effects. Other PIs with CYP3A4 inhibitory activity (atazanavir and atazanavir/ritonavir) resulted in elevated levels of buprenorphine and norbuprenorphine and patients in one study reported increased sedation. Symptoms of opioid excess have been found in post-marketing reports of patients receiving buprenorphine and atazanavir with and without ritonavir concomitantly. Monitoring of patients taking buprenorphine and atazanavir with and without ritonavir is recommended, and dose reduction of buprenorphine may be warranted.

7.3 Benzodiazepines

There have been a number of post-marketing reports regarding coma and death associated with the concomitant use of buprenorphine and benzodiazepines. In many, but not all, of these cases, buprenorphine was misused by self-injection. Preclinical studies have shown that the combination of benzodiazepines and buprenorphine altered the usual ceiling effect on buprenorphine-induced respiratory depression, making the respiratory effects of buprenorphine appear similar to those of full opioid agonists. SUBOXONE sublingual film should be prescribed with caution to patients taking benzodiazepines or other drugs that act on the CNS, regardless of whether these drugs are taken on the advice of a physician or are being abused/misused. Patients should be warned that it is extremely dangerous to self-administer non-prescribed benzodiazepines while taking SUBOXONE sublingual film, and should also be cautioned to use benzodiazepines concurrently with SUBOXONE sublingual film only as directed by their physician.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C.

There are no adequate and well-controlled studies of SUBOXONE sublingual film or buprenorphine/naloxone in pregnant women. SUBOXONE sublingual film should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Teratogenic Effects:

Effects on embryo-fetal development were studied in Sprague-Dawley rats and Russian white rabbits following oral (1:1) and intramuscular (IM) (3:2) administration of mixtures of buprenorphine and naloxone. Following oral administration to rats and rabbits, no teratogenic effects were observed at buprenorphine doses up to 250 mg/kg/day and 40 mg/kg/day, respectively (estimated exposure approximately 150 times and 50 times, respectively, the recommended human daily sublingual dose of 16 mg on a mg/m² basis). No definitive drug-related teratogenic effects were observed in rats and rabbits at IM doses up to 30 mg/kg/day (estimated exposure approximately 20 times and 35 times, respectively, the recommended human daily dose of 16 mg on a mg/m² basis). Acephalus was observed in one rabbit fetus from the low-dose group and omphalocele was observed in two rabbit fetuses from the same litter in the mid-dose group; no findings were observed in fetuses from the high-dose group. Following oral administration of buprenorphine to rats, dose-related post-implantation losses, evidenced by increases in the numbers of early resorptions with consequent reductions in the numbers of fetuses, were observed at doses of 10 mg/kg/day or greater (estimated exposure approximately 6 times the recommended human daily sublingual dose of 16 mg on a mg/m² basis). In the rabbit, increased post-implantation losses occurred at an oral dose of 40 mg/kg/day. Following IM administration in the rat and the rabbit, post-implantation losses, as evidenced by decreases in live fetuses and increases in resorptions, occurred at 30 mg/kg/day.

Buprenorphine was not teratogenic in rats or rabbits after IM or subcutaneous (SC) doses up to 5 mg/kg/day (estimated exposure was approximately 3 and 6 times, respectively, the recommended human daily sublingual dose of 16 mg on a mg/m² basis), after IV doses up to 0.8 mg/kg/day (estimated exposure was approximately 0.5 times and equal to, respectively, the recommended human daily sublingual dose of 16 mg on a mg/m² basis), or after oral doses up to 160 mg/kg/day in rats (estimated exposure was approximately 95 times the recommended human daily sublingual dose of 16 mg on a mg/m² basis) and 25 mg/kg/day in rabbits (estimated exposure was approximately 30 times the recommended human daily sublingual dose of 16 mg on a mg/m² basis). Significant increases in skeletal abnormalities (e.g., extra thoracic vertebra or thoraco-lumbar ribs) were noted in rats after SC administration of 1 mg/kg/day and up (estimated exposure was approximately 0.6 times the recommended human daily sublingual dose of 16 mg on a mg/m² basis), but were not observed at oral doses up to 160 mg/kg/day. Increases in skeletal abnormalities in rabbits after IM administration of 5 mg/kg/day (estimated exposure was approximately 6 times the recommended human daily sublingual dose of 16 mg on a mg/m² basis) or oral administration of 1 mg/kg/day or greater (estimated exposure was approximately equal to the recommended human daily sublingual dose of 16 mg on a mg/m² basis) were not statistically significant.

In rabbits, buprenorphine produced statistically significant pre-implantation losses at oral doses of 1 mg/kg/day or greater and post-implantation losses that were statistically significant at IV doses of 0.2 mg/kg/day or greater (estimated exposure approximately 0.3 times the recommended human daily sublingual dose of 16 mg on a mg/m² basis).

Non-teratogenic Effects:

Dystocia was noted in pregnant rats treated intramuscularly with buprenorphine 5 mg/kg/day (approximately 3 times the recommended human daily sublingual dose of 16 mg on a mg/m² basis). Fertility, peri-, and post-natal development studies with buprenorphine in rats indicated increases in neonatal mortality after oral doses of 0.8 mg/kg/day and up (approximately 0.5 times the recommended human daily sublingual dose of 16 mg on a mg/m² basis), after IM doses of 0.5 mg/kg/day and up (approximately 0.3 times the recommended human daily sublingual dose of 16 mg on a mg/m² basis), and after SC doses of 0.1 mg/kg/day and up (approximately 0.06 times the recommended human daily sublingual dose of 16 mg on a mg/m² basis). Delays in the occurrence of righting reflex and startle response were noted in rat pups at an oral dose of 80 mg/kg/day (approximately 50 times the recommended human daily sublingual dose of 16 mg on a mg/m² basis).

8.3 Nursing Mothers

Buprenorphine passes into breast milk. Breast-feeding is not advised in mothers treated with buprenorphine products.

An apparent lack of milk production during general reproduction studies with buprenorphine in rats caused decreased viability and lactation indices.

8.4 Pediatric Use

The safety and effectiveness of SUBOXONE sublingual film have not been established in pediatric patients.

8.5 Geriatric Use

Clinical studies of SUBOXONE sublingual film, SUBOXONE (buprenorphine and naloxone) sublingual tablets, or SUBUTEX (buprenorphine) sublingual tablets did not include sufficient numbers of subjects aged 65 and over to determine whether they responded differently than younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

8.6 Hepatic Impairment

The effect of hepatic impairment on the pharmacokinetics of buprenorphine and naloxone is unknown. Since both drugs are extensively metabolized, the plasma levels will be expected to be higher in patients with moderate and severe hepatic impairment. However, it is not known whether both drugs are affected to the same degree. Therefore, dosage should be adjusted and patients should be watched for signs and symptoms of precipitated opioid withdrawal.

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8.7 Renal Impairment

No differences in buprenorphine pharmacokinetics were observed between 9 dialysis-dependent and 6 normal patients following IV administration of 0.3 mg buprenorphine. The effects of renal failure on naloxone pharmacokinetics are unknown.

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

Buprenorphine is a Schedule III narcotic under the Controlled Substances Act.

Under the Drug Addiction Treatment Act (DATA) codified at 21 U.S.C. 823(g), prescription use of this product in the treatment of opioid dependence is limited to physicians who meet certain qualifying requirements, and who have notified the Secretary of Health and Human Services (HHS) of their intent to prescribe this product for the treatment of opioid dependence and have been assigned a unique identification number that must be included on every prescription.

9.2 Abuse

Buprenorphine, like morphine and other opioids, has the potential for being abused and is subject to criminal diversion. This should be considered when prescribing or dispensing buprenorphine in situations when the clinician is concerned about an increased risk of misuse, abuse, or diversion. Healthcare professionals should contact their state professional licensing board or state controlled substances authority for information on how to prevent and detect abuse or diversion of this product.

Patients who continue to misuse, abuse, or divert buprenorphine products or other opioids should be provided with or referred for more intensive and structured treatment.

Abuse of buprenorphine poses a risk of overdose and death. This risk is increased with the abuse of buprenorphine and alcohol and other substances, especially benzodiazepines.

The physician may be able to more easily detect misuse or diversion by maintaining records of medication prescribed including date, dose, quantity, frequency of refills, and renewal requests of medication prescribed.

Proper assessment of the patient, proper prescribing practices, periodic re-evaluation of therapy, and proper handling and storage of the medication are appropriate measures that help to limit abuse of opioid drugs.

9.3 Dependence

Buprenorphine is a partial agonist at the mu-opioid receptor and chronic administration produces physical dependence of the opioid type, characterized by moderate withdrawal signs and symptoms upon abrupt discontinuation or rapid taper. The withdrawal syndrome is typically milder than seen with full agonists and may be delayed in onset *[see Warnings and Precautions (5.5)]*.

A neonatal withdrawal syndrome has been reported in the infants of women treated with buprenorphine during pregnancy *[see Warnings and Precautions (5.9)]*.

10 OVERDOSAGE

The manifestations of acute overdose include pinpoint pupils, sedation, hypotension, respiratory depression, and death.

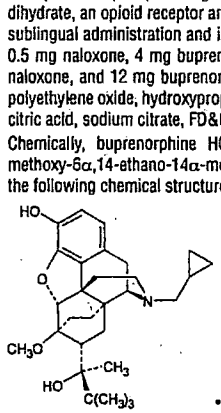
In the event of overdose, the respiratory and cardiac status of the patient should be monitored carefully. When respiratory or cardiac functions are depressed, primary attention should be given to the re-establishment of adequate respiratory exchange through provision of a patent airway and institution of assisted or controlled ventilation. Oxygen, IV fluids, vasopressors, and other supportive measures should be employed as indicated.

In the case of overdose, the primary management should be the re-establishment of adequate ventilation with mechanical assistance of respiration, if required. Naloxone may be of value for the management of buprenorphine overdose. Higher than normal doses and repeated administration may be necessary.

11 DESCRIPTION

SUBOXONE (buprenorphine and naloxone) sublingual film is an orange film, imprinted with a logo identifying the product and strength in white ink. It contains buprenorphine HCl, a mu-opioid receptor partial agonist and a kappa-opioid receptor antagonist, and naloxone HCl dihydrate, an opioid receptor antagonist, at a ratio of 4:1 (ratio of free bases). It is intended for sublingual administration and is available in four dosage strengths, 2 mg buprenorphine with 0.5 mg naloxone, 4 mg buprenorphine with 1 mg naloxone, 8 mg buprenorphine with 2 mg naloxone, and 12 mg buprenorphine with 3 mg naloxone. Each sublingual film also contains polyethylene oxide, hydroxypropyl methylcellulose, maltitol, acesulfame potassium, lime flavor, citric acid, sodium citrate, FD&C yellow #6, and white ink.

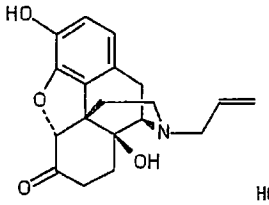
Chemically, buprenorphine HCl is (2S)-2-[17-Cyclopropylmethyl-4,5α-epoxy-3-hydroxy-6-methoxy-6α,14-ethano-14α-morphinan-7α-yl]-3,3-dimethylbutan-2-ol hydrochloride. It has the following chemical structure:



•HCl

Buprenorphine HCl has the molecular formula $C_{29}H_{41}NO_4$ • HCl and the molecular weight is 504.10. It is a white or off-white crystalline powder, sparingly soluble in water, freely soluble in methanol, soluble in alcohol, and practically insoluble in cyclohexane.

Chemically, naloxone HCl dihydrate is 17-Allyl-4,5 α -epoxy-3, 14-dihydroxymorphinan-6-one hydrochloride dihydrate. It has the following chemical structure:



HCl • $2H_2O$

Naloxone hydrochloride dihydrate has the molecular formula $C_{19}H_{21}NO_4$ • HCl • $2H_2O$ and the molecular weight is 399.87. It is a white to slightly off-white powder and is freely soluble in water, soluble in alcohol, and practically insoluble in toluene and ether.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

SUBOXONE sublingual film contains buprenorphine and naloxone. Buprenorphine is a partial agonist at the mu-opioid receptor and an antagonist at the kappa-opioid receptor. Naloxone is a potent antagonist at mu-opioid receptors and produces opioid withdrawal signs and symptoms in individuals physically dependent on full opioid agonists when administered parenterally.

12.2 Pharmacodynamics

Subjective Effects:

Comparisons of buprenorphine to full opioid agonists such as methadone and hydromorphone suggest that sublingual buprenorphine produces typical opioid agonist effects which are limited by a ceiling effect.

In opioid-experienced subjects who were not physically dependent, acute sublingual doses of buprenorphine/naloxone tablets produced opioid agonist effects which reached a maximum between doses of 8 mg/2 mg and 16 mg/4 mg buprenorphine/naloxone.

Opioid agonist ceiling-effects were also observed in a double-blind, parallel group, dose-ranging comparison of single doses of buprenorphine sublingual solution (1, 2, 4, 8, 16, or 32 mg), placebo and a full agonist control at various doses. The treatments were given in ascending dose order at intervals of at least one week to 16 opioid-experienced subjects who were not physically dependent. Both active drugs produced typical opioid agonist effects. For all measures for which the drugs produced an effect, buprenorphine produced a dose-related response. However, in each case, there was a dose that produced no further effect. In contrast, the highest dose of the full agonist control always produced the greatest effects. Agonist objective rating scores remained elevated for the higher doses of buprenorphine (8-32 mg) longer than for the lower doses and did not return to baseline until 48 hours after drug administration. The onset of effects appeared more rapidly with buprenorphine than with the full agonist control, with most doses nearing peak effect after 100 minutes for buprenorphine compared to 150 minutes for the full agonist control.

Physiologic Effects:

Buprenorphine in IV (2, 4, 8, 12 and 16 mg) and sublingual (12 mg) doses has been administered to opioid-experienced subjects who were not physically dependent to examine cardiovascular, respiratory, and subjective effects at doses comparable to those used for treatment of opioid dependence. Compared to placebo, there were no statistically significant differences among any of the treatment conditions for blood pressure, heart rate, respiratory rate, O_2 saturation, or skin temperature across time. Systolic BP was higher in the 8 mg group than placebo (3-hour AUC values). Minimum and maximum effects were similar across all treatments. Subjects remained responsive to low voice and responded to computer prompts. Some subjects showed irritability, but no other changes were observed.

The respiratory effects of sublingual buprenorphine were compared with the effects of methadone in a double-blind, parallel group, dose ranging comparison of single doses of buprenorphine sublingual solution (1, 2, 4, 8, 16, or 32 mg) and oral methadone (15, 30, 45, or 60 mg) in non-dependent, opioid-experienced volunteers. In this study, hypoventilation not requiring medical intervention was reported more frequently after buprenorphine doses of 4 mg and higher than after methadone. Both drugs decreased O_2 saturation to the same degree.

Effect of Naloxone:

Physiologic and subjective effects following acute sublingual administration of buprenorphine tablets and buprenorphine/naloxone tablets were similar at equivalent dose levels of buprenorphine. Naloxone had no clinically significant effect when administered by the sublingual route, although blood levels of the drug were measurable. Buprenorphine/naloxone, when administered sublingually to an opioid-dependent cohort, was recognized as an opioid agonist, whereas when administered intramuscularly, combinations of buprenorphine with naloxone produced opioid antagonist actions similar to naloxone. This finding suggests that the naloxone in buprenorphine/naloxone tablets may deter injection of buprenorphine/naloxone tablets by persons with active substantial heroin or other full mu-opioid dependence. However, clinicians should be aware that some opioid-dependent persons, particularly those with a low level of full mu-opioid physical dependence or those whose opioid physical dependence is predominantly to buprenorphine, abuse buprenorphine/naloxone combinations by the intravenous or intranasal route. In methadone-maintained patients and heroin-dependent subjects, IV administration of buprenorphine/naloxone combinations precipitated opioid withdrawal signs and symptoms and was perceived as unpleasant and dysphoric. In morphine-stabilized subjects, intravenously administered combinations of buprenorphine with naloxone produced opioid antagonist and withdrawal signs and symptoms that were ratio-dependent; the most intense withdrawal signs and symptoms were produced by 2:1 and 4:1 ratios, less intense by an 8:1 ratio.

12.3 Pharmacokinetics

Absorption:

In pharmacokinetic studies, the 2 mg/0.5 mg and 4 mg/1 mg doses administered as SUBOXONE sublingual films showed comparable relative bioavailability to the same total dose of SUBOXONE sublingual tablets, whereas the 8 mg/2 mg and 12 mg/3 mg doses administered as SUBOXONE sublingual films showed higher relative bioavailability for both buprenorphine and naloxone compared to the same total dose of SUBOXONE sublingual tablets. A combination

EXHIBIT C

of one 8 mg/2 mg and two 2 mg/0.5 mg SUBOXONE sublingual films (total dose of 12 mg/3 mg) showed comparable relative bioavailability to the same total dose of SUBOXONE sublingual tablets *[See Dosage and Administration (2.6 and 2.7)]*.

Distribution:

Buprenorphine is approximately 96% protein bound, primarily to alpha and beta globulin.

Naloxone is approximately 45% protein bound, primarily to albumin.

Metabolism:

Buprenorphine undergoes both N-dealkylation to norbuprenorphine and glucuronidation. The N-dealkylation pathway is mediated primarily by the CYP3A4. Norbuprenorphine, the major metabolite, can further undergo glucuronidation. Norbuprenorphine has been found to bind opioid receptors *in-vitro*; however, it has not been studied clinically for opioid-like activity. Naloxone undergoes direct glucuronidation to naloxone-3-glucuronide as well as N-dealkylation, and reduction of the 6-oxo group.

Elimination:

A mass balance study of buprenorphine showed complete recovery of radiolabel in urine (30%) and feces (69%) collected up to 11 days after dosing. Almost all of the dose was accounted for in terms of buprenorphine, norbuprenorphine, and two unidentified buprenorphine metabolites. In urine, most of buprenorphine and norbuprenorphine was conjugated (buprenorphine, 1% free and 9.4% conjugated; norbuprenorphine, 2.7% free and 11% conjugated). In feces, almost all of the buprenorphine and norbuprenorphine were free (buprenorphine, 33% free and 5% conjugated; norbuprenorphine, 21% free and 2% conjugated). Based on all studies performed with SUBOXONE sublingual film, buprenorphine has a mean elimination half-life from plasma ranging from 24 to 42 hours and naloxone has a mean elimination half-life from plasma ranging from 2 to 12 hours.

Drug-drug Interactions:

CYP3A4 Inhibitors and Inducers: Subjects receiving SUBOXONE sublingual film should be monitored if inhibitors of CYP3A4 such as azole antifungal agents (e.g., ketoconazole), macrolide antibiotics (e.g., erythromycin) or HIV protease inhibitors and may require dose-reduction of one or both agents. The interaction of buprenorphine with all CYP3A4 inducers has not been studied, therefore it is recommended that patients receiving SUBOXONE sublingual film be monitored for signs and symptoms of opioid withdrawal if inducers of CYP3A4 (e.g., phenobarbital, carbamazepine, phenytoin, rifampicin) are co-administered *[See Drug Interactions (7.1)]*.

Buprenorphine has been found to be a CYP2D6 and CYP3A4 inhibitor and its major metabolite, norbuprenorphine, has been found to be a moderate CYP2D6 inhibitor in *in-vitro* studies employing human liver microsomes. However, the relatively low plasma concentrations of buprenorphine and norbuprenorphine resulting from therapeutic doses are not expected to raise significant drug-drug interaction concerns.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity:

Carcinogenicity data on SUBOXONE sublingual film are not available.

A carcinogenicity study of buprenorphine/naloxone (4:1 ratio of the free bases) was performed in Alderley Park rats. Buprenorphine/naloxone was administered in the diet at doses of approximately 7, 31, and 123 mg/kg/day for 104 weeks (estimated exposure was approximately 4, 18, and 44 times the recommended human sublingual dose of 16 mg/4 mg buprenorphine/naloxone based on buprenorphine AUC comparisons). A statistically significant increase in Leydig cell adenomas was observed in all dose groups. No other drug-related tumors were noted.

Carcinogenicity studies of buprenorphine were conducted in Sprague-Dawley rats and CD-1 mice. Buprenorphine was administered in the diet to rats at doses of 0.6, 5.5, and 56 mg/kg/day (estimated exposure was approximately 0.4, 3, and 35 times the recommended human daily sublingual dose of 16 mg on a mg/m² basis) for 27 months. As in the buprenorphine/naloxone carcinogenicity study in rat, statistically significant dose-related increases in Leydig cell tumors occurred. In an 86-week study in CD-1 mice, buprenorphine was not carcinogenic at dietary doses up to 100 mg/kg/day (estimated exposure was approximately 30 times the recommended human daily sublingual dose of 16 mg on a mg/m² basis).

Mutagenicity:

The 4:1 combination of buprenorphine and naloxone was not mutagenic in a bacterial mutation assay (Ames test) using four strains of *S. typhimurium* and two strains of *E. coli*. The combination was not clastogenic in an *in-vitro* cytogenetic assay in human lymphocytes or in an IV micronucleus test in the rat.

Buprenorphine was studied in a series of tests utilizing gene, chromosome, and DNA interactions in both prokaryotic and eukaryotic systems. Results were negative in yeast (*S. cerevisiae*) for recombinant, gene convertant, or forward mutations; negative in *Bacillus subtilis* "rec" assay, negative for clastogenicity in CHO cells, Chinese hamster bone marrow and spermatogonia cells, and negative in the mouse lymphoma L5178Y assay.

Results were equivocal in the Ames test: negative in studies in two laboratories, but positive for frame shift mutation at a high dose (5 mg/plate) in a third study. Results were positive in the Green-Tweets (*E. coli*) survival test, positive in a DNA synthesis inhibition (DSI) test with testicular tissue from mice, for both *in-vivo* and *in-vitro* incorporation of [³H]thymidine, and positive in unscheduled DNA synthesis (UDS) test using testicular cells from mice.

Impairment of Fertility:

Dietary administration of buprenorphine in the rat at dose levels of 500 ppm or greater (equivalent to approximately 47 mg/kg/day or greater; estimated exposure approximately 28 times the recommended human daily sublingual dose of 16 mg on a mg/m² basis) produced a reduction in fertility demonstrated by reduced female conception rates. A dietary dose of 100 ppm (equivalent to approximately 10 mg/kg/day; estimated exposure approximately 6 times the recommended human daily sublingual dose of 16 mg on a mg/m² basis) had no adverse effect on fertility.

16 HOW SUPPLIED / STORAGE AND HANDLING

SUBOXONE sublingual film is supplied as an orange rectangular sublingual film with a white printed logo in child-resistant polyester/foil laminated pouches:

- NDC 12496-1202-3 (buprenorphine/naloxone 2 mg/0.5 mg/film; content expressed in terms of free base) - 30 films per carton
- NDC 12496-1204-3 (buprenorphine/naloxone 4 mg/1 mg/film; content expressed in terms of free base) - 30 films per carton
- NDC 12496-1208-3 (buprenorphine/naloxone 8 mg/2 mg/film; content expressed in terms of free base) - 30 films per carton
- NDC 12496-1212-3 (buprenorphine/naloxone 12 mg/3 mg/film; content expressed in terms of free base) - 30 films per carton

Store at 25°C (77°F), excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature]

Patients should be advised to store buprenorphine-containing medications safely and out of sight and reach of children.

Rx only

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Medication Guide)

Patients should be advised NOT to cut, chew or swallow SUBOXONE sublingual film.

17.1 Safe Use

Before initiating treatment with SUBOXONE, explain the points listed below to caregivers and patients. Instruct patients to read the Medication Guide each time SUBOXONE is dispensed because new information may be available.

- Patients should be warned that it is extremely dangerous to self-administer non-prescribed benzodiazepines or other CNS depressants (including alcohol) while taking SUBOXONE sublingual film. Patients prescribed benzodiazepines or other CNS depressants should be cautioned to use them only as directed by their physician. *[see Warnings and Precautions (5.2), Drug Interactions (7.3)]*
- Patients should be advised that SUBOXONE sublingual film contains an opioid that can be a target for people who abuse prescription medications or street drugs. Patients should be cautioned to keep their films in a safe place, and to protect them from theft.
- Patients should be instructed to keep SUBOXONE sublingual film in a secure place, out of the sight and reach of children. Accidental or deliberate ingestion by a child may cause respiratory depression that can result in death. Patients should be advised that if a child is exposed to SUBOXONE sublingual film, medical attention should be sought immediately.
- Patients should be advised never to give SUBOXONE sublingual film to anyone else, even if he or she has the same signs and symptoms. It may cause harm or death.
- Patients should be advised that selling or giving away this medication is against the law.
- Patients should be cautioned that SUBOXONE sublingual film may impair the mental or physical abilities required for the performance of potentially dangerous tasks such as driving or operating machinery. Caution should be taken especially during drug induction and dose adjustment and until individuals are reasonably certain that buprenorphine therapy does not adversely affect their ability to engage in such activities. *[see Warnings and Precautions (5.11)]*
- Patients should be advised not to change the dosage of SUBOXONE sublingual film without consulting their physician.
- Patients should be advised to take SUBOXONE sublingual film once a day.
- Patients should be informed that SUBOXONE sublingual film can cause drug dependence and that withdrawal signs and symptoms may occur when the medication is discontinued.
- Patients seeking to discontinue treatment with buprenorphine for opioid dependence should be advised to work closely with their physician on a tapering schedule and should be apprised of the potential to relapse to illicit drug use associated with discontinuation of opioid agonist/partial agonist medication-assisted treatment.
- Patients should be cautioned that, like other opioids, SUBOXONE sublingual film may produce orthostatic hypotension in ambulatory individuals. *[see Warnings and Precautions. (5.12)]*
- Patients should inform their physician if any other prescription medications, over-the-counter medications, or herbal preparations are prescribed or currently being used. *[see Drug Interactions (7.1, 7.2 and 7.3)]*
- Women of childbearing potential who become pregnant or are planning to become pregnant, should be advised to consult their physician regarding the possible effects of using SUBOXONE sublingual film during pregnancy. *[see Use in Specific Populations (8.1)]*
- Patients should be warned that buprenorphine passes into breast milk. Breast-feeding is not advised in mothers treated with buprenorphine products. *[see Use in Specific Populations (8.3)]*.
- Patients should inform their family members that, in the event of emergency, the treating physician or emergency room staff should be informed that the patient is physically dependent on an opioid and that the patient is being treated with SUBOXONE sublingual film.
- Refer to the Medication Guide for additional information regarding the counseling information.

1-1202-019-US-0812

Manufactured for Reckitt Benckiser Pharmaceuticals Inc.,
Richmond, VA 23235 by:
MonoSol Rx, LLC,
Warren, NJ 07059

Distributed by:
Reckitt Benckiser Pharmaceuticals Inc.
Richmond, VA 23235

EXHIBIT D

10/26/2010

Buprenorphine Pilot Project with Parolees in Illinois: Early Results and Lessons Learned

Dona Howell-IDOC Manager of Addiction and Recovery Service
Janelle Prueter, Director-TASC Corrections Program
Arturo Valdez- HAS

GOALS

- Explain the process of gaining acceptance of Medication Assisted Treatment as a viable treatment option within the criminal justice system
- Share the lessons learned as pilot program implementation moved forward
- Identify strategies for improving outcomes for MAT for opiate dependent parolees

PARTNERS

- Reckitt Benckiser Pharmaceutical Company
- HAS- Healthcare Alternative Systems
- TASC- Treatment Alternatives for Safe Communities
- Haymarket
- Westcare
- IDOC-including Sheridan Correctional Center, Parole, Placement Resource Unit, Addiction Management and Recovery Services

EXHIBIT D

10/26/2010

PROCESS

- Building on an existing structure to expand successful programming for IDOC parolees leaving one of the national model programs- Sheridan Correctional Center
- Reentry Program Council
- NIDA- CJDATS Program

PROCESS

- Evaluation of parolee success in the community
- Longitutidinally, Opiate addicts were found to have some of the lowest success rates in the transition from facility based treatment to the community
- Utilization of existing partners, supported by a grant from Reckitt Benckiser to develop alternative programming options

IDOC

- Sheridan has 950 totally dedicated substance abuse treatment beds at Sheridan with another 300 Pre Treatment and 206 Pre Release beds on site for offenders either getting ready to transition to the community or move into the treatment.
- Safer provides job preparedness training, job coaching, and vocational services
- TASC provides the pre release clinical case management and Inner Circle groups on site
- Both Safer and TASC focus the majority of their services toward the end of an offender's stay at Sheridan

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10/26/2010

IDOC

- Already invested in evidence based practices and exploring ways to improve outcomes as offenders transition into the community
- 6 years worth of research on the National Model Treatment Program at Sheridan
- Partnerships between IDOC, TASC, SAFER, HAS, and Haymarket already in existence
- Lessons already learned and shared

IDOC

- Sheridan parolees have a significant amount of services available to them in the community
- TASC provides the clinical case management both pre and post services for Sheridan
- Westcare provides the "in-house" substance abuse treatment for offenders and is part of the process to make clinical continuing care recommendations for offenders paroling to the community

TASC

- Responsible for providing clinical reentry management both pre and post release
- Involved in advocating for medication assisted therapy for offenders struggling with opiate addiction
- The bridge for offenders leaving Sheridan and transitioning to the community
- Monitors parolees' progress in treatment in the community

EXHIBIT D

10/26/2010

TASC

- Advocate for treatment
- Case manager that works with individual parolees to ensure that they follow their discharge summary and help modify programming when things are not working
- Explores with parolees other options for programming
- A partner along with parole, PRU, the community treatment providers, and SAFER

HAS

- A community based substance abuse treatment agency already familiar with both the treatment population and the treatment regime
- HAS has contracts with both IDOC and TASC to provide substance abuse treatment for parolees
- 35 years of experience in the treatment of addiction

HAYMARKET

- Contracted by IDOC to provide an array of treatment services to parolees
- Already using Suboxone in the detoxification of opiate-dependent offenders.

EXHIBIT D

10/26/2010

A New Treatment Model including MAT

- The population included opiate affected former offenders released from Sheridan that relapsed during or following a course of community based treatment.
- Offenders motivated to change and struggling in their recovery.
- TASC staff and/or parole agents meet with the offender to talk about the option for treatment combined with MAT-suboxone.

A New Treatment Model including MAT

- Those that agreed to participate in the pilot either entered detox at Haymarket or began induction to suboxone at HAS.
- Treatment services and medication management conducted by HAS.
- TASC continues to provide intensive case management services coupled with supervision by parole.

THE PROCESS

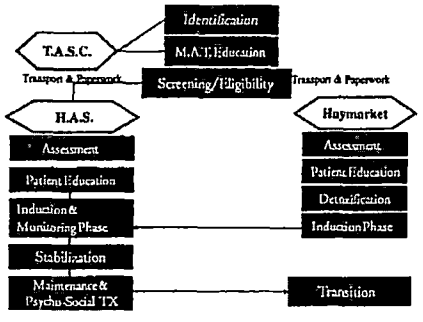
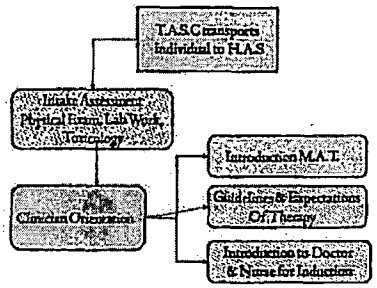


EXHIBIT D

10/26/2010

Patient Education



Suboxone Induction & Stabilization

- Administered when an opioid-addicted individual has mild to moderate withdrawal symptoms
- Individual is seen by the Doctor and Nurse for first dose in the office
- Individual is then assessed immediately or within a few hours of effects
- Prescription is given extending until the next appointment
- Adjustment period until stabilized
- Enter patient education and psycho-social phase

Outpatient Psychosocial Treatment

I. *Thinking for Change*
- National Institute of Corrections Cognitive Behavioral Curriculum

II. *Strategies for Self-Improvement and Change (SSC)*
(Wanberg & Milkman Criminal Conduct and Substance Abuse Treatment)
- Chemical dependency Treatment I
- Criminogenic Risk and Needs Emphasis

III. *Relapse Prevention* (Wanberg & Milkman Criminal Conduct and Substance Abuse Treatment)

EXHIBIT D

10/26/2010

CASE STUDY

47 year old African American Male:

Recovery Capital: sober living environment, participated in 12 step groups, tested negative at treatment assessment; part-time employment, some family support

Characteristics of Drug Challenges:

- 20 year history heroin/cocaine use
- Relapsed 5 months post release
- 3rd treatment episode within 13 months
- Acute episodes of depression

Process

-February 10th referral communication from TASC
- Seen by HAS next day
-Induction 1st dose 8 mg February 11th (inclusive of assessment, physical)
- 2 more doctor follow ups
- Treatment participation started March 15th did not complete due to ongoing transportation issues. Completed 55 hours of treatment

CASE STUDY

Prior case continued:

Current status:

Client continues on suboxone and has had some ups and downs related to continued use. Mostly recently is drug free and continuing suboxone.

CASE STUDY

40 year old African American Male:

Reason for Referral: Client was AWOL from parole and TASC for 3 months. When found, admitted daily use of opiates.

Recovery Capital:

Married 14 years, high school diploma, primary care doctor, high level of awareness of drug challenges, previous successful treatment completions, employment skills, also aware of triggers. Engaged in process and willingness to participate.

Characteristics of Drug Challenges:

13 year heroin use history

Client dropped out suddenly after completing 15 hours of treatment and taking suboxone consistently

EXHIBIT D

10/26/2010

CASE STUDY

- Inducted into the Suboxone program March of 2010.
- Struggled initially with both treatment compliance and abstaining from other drugs (cocaine and marijuana);
- Admitted to Detox at Haymarket; and stepped down through Haymarket 's Residential Program for 28 days and then to Haymarket's CIP Program (90 day recovery home).
- Participant has since been stepped down on his medication dosage, to where now, he no longer takes Suboxone.
- He suggested a Suboxone Support Group for the clients currently in the program stating they have similar backgrounds (drug and criminal) which currently meets one time per week.
- Participant completed treatment at H.A.S. and has begun working with the Department of Streets and Sanitation.

LESSONS LEARNED

- Educating all involved systems, staff and offenders on the role, purpose, and intentions of MAT is critical.
- Understanding the role and significance of treatment combined within MAT needs to be defined early on in the process.
- Continuity of contact over time with all team members and participant is vital to prevention, intervention, and ongoing participation.

LESSONS LEARNED

- Focus on a very difficult to treat population that had already relapsed and in jeopardy of returning to prison.

EXHIBIT D

10/26/2010

NEXT STEPS

- Modify criteria to determine most appropriate participants for the program
- Introduce program and educate potential participants while in reentry phase of incarceration.
- Introduce MAT combined with appropriate treatment services immediately following release from prison
- Increase education to participants , their families and staff regarding MAT

Next Steps

- Increase resources and expand recovery initiation and planning for participants within the community to address the multiple challenges people face such as vocational training, education, employment, housing, and recreation.

NEXT STEPS

- Create a more efficient data access system to the participants file by all partners.
- Create an participant advisory council comprised of current and discharged MAT clients to serve as adjuncts to direct service staff (peers).
- Increase telephone recovery check ins and follow up (rapid, assertive, and ongoing engagement and communication).

EXHIBIT D

EXHIBIT E

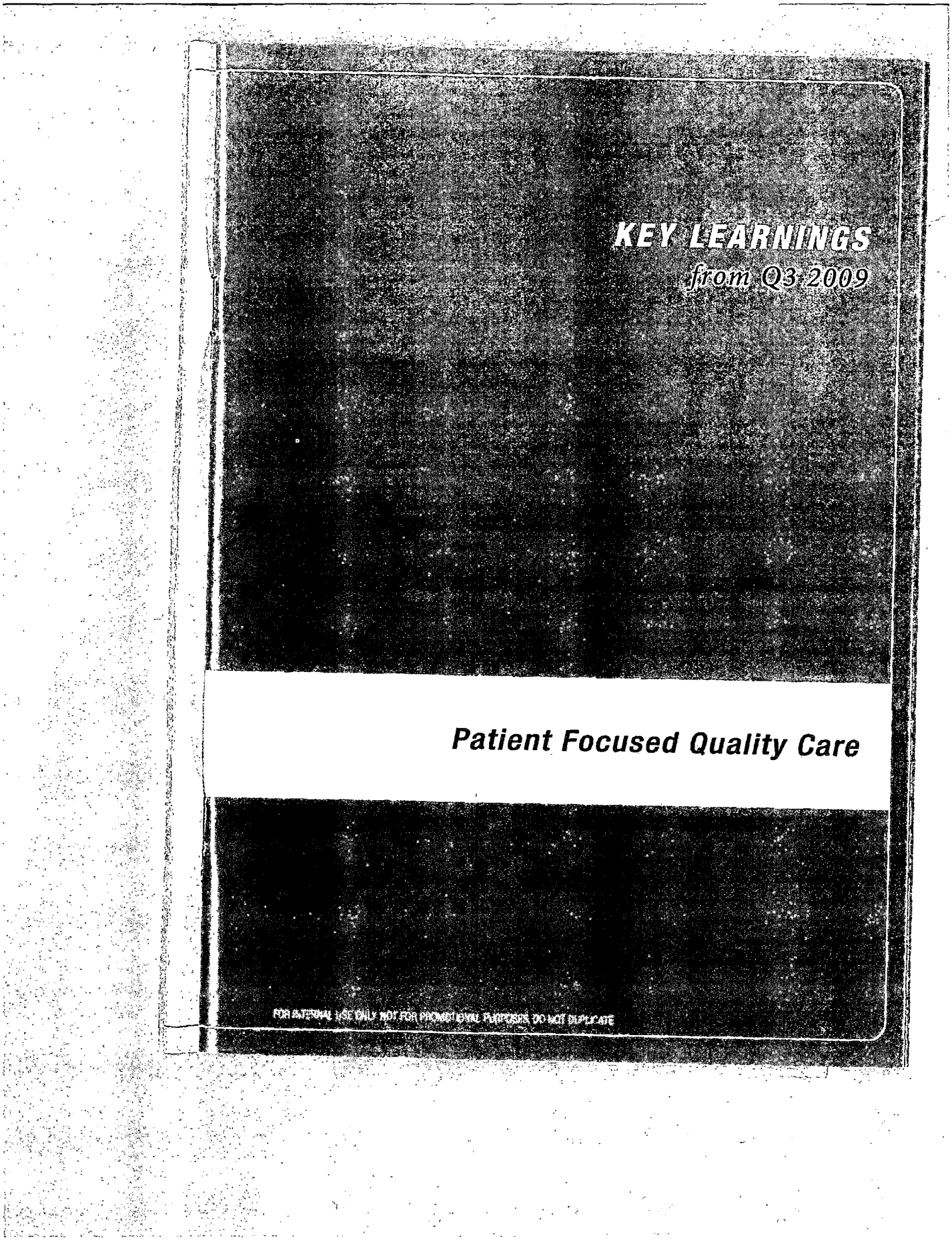

KEY LEARNINGS
from Q3 2009
Patient Focused Quality Care
FOR INTERNAL USE ONLY NOT FOR PROMOTIONAL PURPOSES DO NOT DUPLICATE

EXHIBIT E

Key Learnings from Q3 2009

Your efforts in promoting the Here to Help® program have further demonstrated Reckitt Benckiser Pharmaceuticals' commitment to the treatment of opioid dependence and Patient Focused Quality Care by addressing the many barriers that physicians and patients experience.

We have built a strong foundation with Here to Help® providers, physicians, and counselors. You are building their hands-on experience with the difference Here to Help® makes for their patients. Patient enrollment in the Here to Help® program continues to grow as of October 5, 2009:

- Over **12,971** Patients have been assisted in finding treatment through Here to Help®
- **3,885** Patients have enrolled in Here to Help®
  - ***2,648 patients have completed at least one Care Coach call***
  - ***1,237 patients have enrolled in email support through a Care Coordinator***
- Another **1,275** patients enrolled in Here to Help® email through the website

The value the Here to Help® program provides is evident in the feedback we are receiving from both physicians and patients. Physicians with enrolled patients actively engaged in the Here to Help® program are able to recognize the benefits the program brings to their patients and their practice.

- "We tell our patients that if they have a question after office hours or on weekends, to call their Care Coach first, write down the information or concern in their Everyday Success Planner, and then bring it in to their next appointment. This has worked well for them and has cut back on after-hour paging to the doctor and calls to the office."
- "I have been reluctant to expand beyond 30 patients because these patients demand a lot from my staff in terms of phone time, education and treatment follow up. The Here to Help® program will provide me with the kind of resource that I now believe I can increase my number of patients to 55-60."
- "I like having this program Here to Help® available because I feel like I have the assurance that I could always talk to somebody and that's better than to fall back."

EXHIBIT E

Key Learnings from Q3 2009

Key Learnings (continued):

It is important for all of your physicians to experience the positive impact Here to Help® can have on their patients and their practice. As each new patient experiences the benefits of Here to Help®, it becomes an indispensible part of treatment and further reinforces the important contribution that RBP is making to promote *Patient Focused Quality Care.*

[Notes]

EXHIBIT E

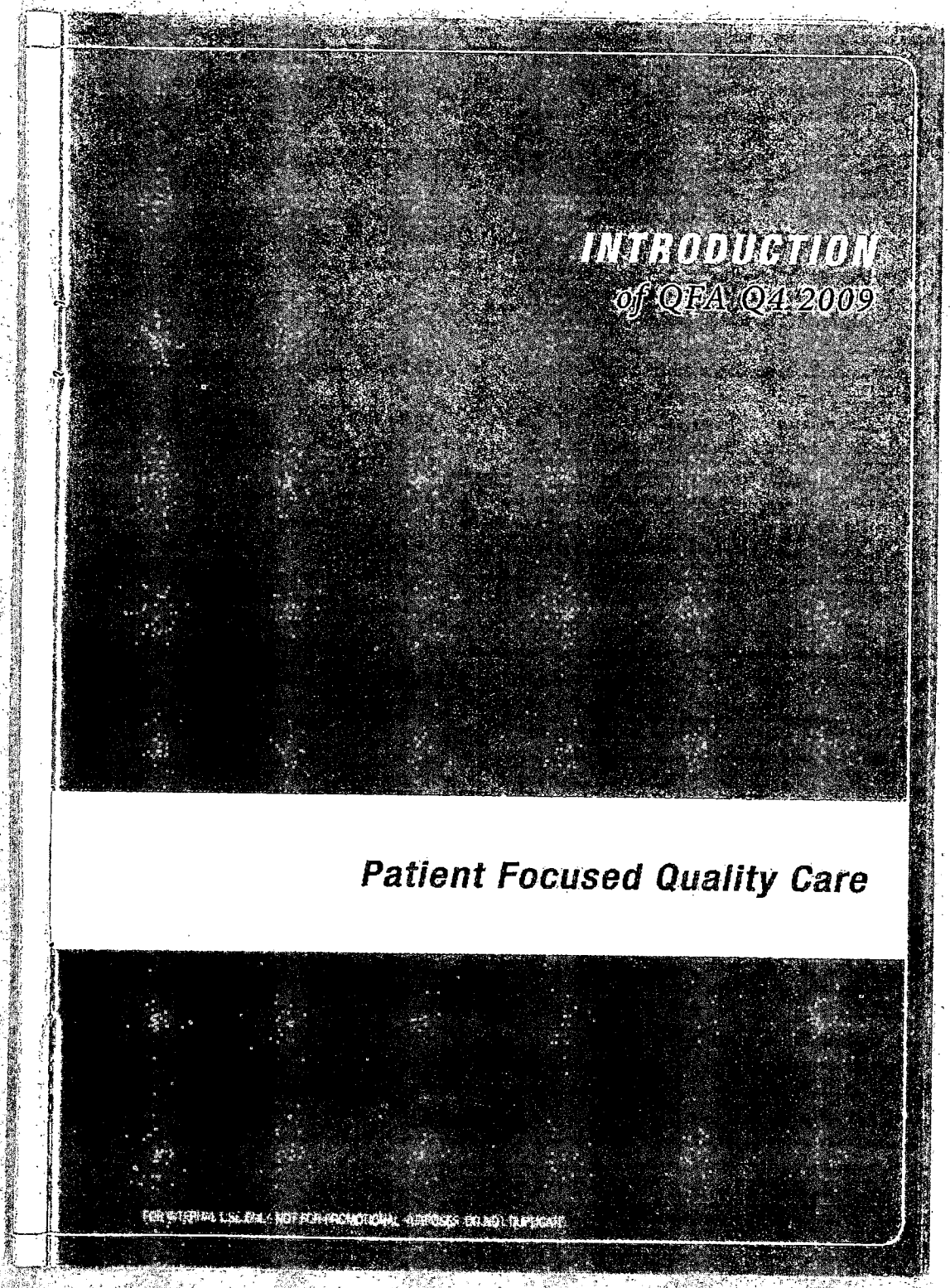


EXHIBIT E

Introduction to QFA Q4 2009

As Clinical Liaisons, you are trusted advisors to many of your physicians because of your ongoing commitment to improving the lives of patients by advocating for Patient Focused Quality Care beyond just the medication.

The last two quarters have focused on introducing Here to Help® and promoting the value of the program to improve the quality of care for opioid dependence. We need to continue to build upon these efforts by reinforcing the value that you bring to your matrix members through the promotion of SUBOXONE® (buprenorphine and naloxone) + Counseling + Here to Help® as the new model of Patient Focused Quality Care. Your efforts will make SUBOXONE® synonymous with quality care and further strengthen our brand equity.

This effort is critical given that our marketplace has expanded to include a generic buprenorphine-only product. On October 9, 2009, Roxane Laboratories received FDA approval for generic Subutex® (buprenorphine) sublingual tablets CIII. Following the recent approval of this generic buprenorphine tablet there will likely be a push from patients to request a switch from SUBOXONE® to generic buprenorphine - only to reduce their medication costs. Physicians may be likely to comply with this request if they do not understand the importance or value of the naloxone component of SUBOXONE® to their patients and their practice, and the value of the Here to Help® program.

Now and in the future it is critical that your physicians understand and believe in the role that SUBOXONE® and Here to Help® play to ensure Patient Focused Quality Care.

Care Coordination: Successfully Opening Up Access to Care

- In the first 6 months*, HTH Care Coordinators helped 18,692 people connect with a physician's office
- Currently ~2400 patients per week call the HTH line seeking treatment
- An additional ~16,000 people per week use the online HTH locator

*HTH launched 4/27/09

Suboxone (buprenorphine HCl/naloxone HCl dihydrate) C-III

Care Coordination: Providing Value to Enrolled Physicians

"A Care Coordinator called in with the patient, stayed on the line to introduce the patient, then left the line. The patient and I talked for a short while and an appointment was set up for next week for the patient to come to the office. I was impressed with the knowledge the patient had about Suboxone and her openness about her disease. If [Here to Help] is able to help bring patients to me like this, I will continue accepting new patients." - HTH enrolled physician

"I've had patients come from two hours away and they are being referred to me through Here to Help®, and so that's been a very good resource." - Dr Gregory Dobash

Suboxone®

EXHIBIT F

Here to Help® Care Coordination

- Here to Help (HTH) Care Coordinators help patients find treatment and encourage them to access it
- Care Coordinators provide
  - Up-to-date information on HTH enrolled treatment providers
  - Assistance in making the first appointment
  - Follow-up with patient that an appointment has been scheduled
  - Enrollment in Here to Help Care Coaching
  - Support in overcoming the barriers to finding treatment
  - Referrals to email support and internet resources
- These services are designed to increase the likelihood that the patient makes and keeps their first appointment

Suboxone

How can you ensure that your patients benefit from Here to Help®?

- How can we work together to facilitate more patients enroll in HTH?
- How can we make sure they are engaged in HTH?

"Now if I have patients who are kind of reluctant to use Here to Help, I'm wondering how seriously they're taking their treatment. Patients who are using Here to Help want to do the extra things it takes." – Dr. Brian Rodgers

Suboxone

Accessing Treatment is Only the First Step

- Once in treatment, patients face additional barriers to being successful in treatment
  - Lack of ongoing support
  - Lack of personalized resources to help them take a more active role in their treatment and be successful
  - Lack of support outside office hours and on weekends

- Here to Help® Care Coaching is designed to assist patients in overcoming the barriers to treatment success

Suboxone
(buprenorphine HCl and naloxone HCl dihydrate) CII

EXHIBIT G

Counselor's Clinical Cottage, PSC

1205 MONTGOMERY PLAZA, SUITE # 3
ASHLAND, KY 41101
PH: 606-329-0727 FX: 606-329-1327
BUSINESS LICENSE ID# BL-2011-12
GROUP NPI # 1831366327

Jade A. Maddox, MA, LPCC, NCC / Executive Director /
Past President of the Kentucky Counselor's Association

Dr. Rodney Crock, Board Certified Family Practice, Expect in Chemical Dependency Treatment
DEA XC # XC832464, NPI # 1891738357

April 4, 2013

To Whom It May Concern:

The preferred medication (buprenorphine and naloxone tablet) that is recommended by this patient's insurance company is not acceptable.

This tablet is unacceptable due to patient risk of misuse, abuse, and diversion. I am recommending the patient use Suboxone Sublingual Film Therapy.

Sincerely,

Dr. Rodney Crock